INTRODUCTION

INTRODUCTION

Over the past decade, significant research has been conducted regarding the physiologic role and expression of cyclooxygenase isoforms 1 and 2 and knowledge in this area is continually evolving. The majority of available data are from animal models, and therefore may not be readily translatable to humans. Early in the 1990s, when COX-2 was first identified, it became apparent that COX-2 was primarily inducible as a component of inflammatory reactions, whereas COX-1 was primarily constitutive and involved in "housekeeping" functions. Since then, research has shown that this theory is truly oversimplified and that the separation of roles and functions of these isoenzymes is far from clear. Because the specific roles of COX-1 and COX-2 are still incompletely understood, cyclooxygenase selectivity profiles are of unknown value in predicting the effects of individual agents during clinical use and, in particular, in suggesting clinical superiority or absence of effect on clinical parameters such as renal function or ulcer formation.

Although it cannot be concluded that cyclooxygenase selectivity has no role in the activity or adverse-event profile of a particular agent, COX-2 selectivity does not guarantee clinical efficacy or safety. This document provides the Agency and the Arthritis Advisory Committee with a resource that reviews available literature and provides additional perspectives that may assist in regulatory review of selective COX-2 inhibitors. The data contained herein support the conclusion that the original COX-1/COX-2 hypothesis is oversimplified and that clinical data are still necessary to assess the adverse-event profile of any given agent. Further, the following summary provides preclinical evidence that the Agency may wish to pursue with regard to the potential safety of agents that specifically inhibit COX-2.

ROLE OF COX-1 AND COX-2

IN INFLAMMATION

ROLE OF COX-1 AND COX-2 IN INFLAMMATION

During inflammation, COX-2 clearly is upregulated (Crofford, 1997). Animal models demonstrate expression of COX-2 during acute and chronic inflammation (Anderson et al, 1996; Sano et al, 1992). Treatment with glucocorticoids and specific COX-2 inhibitors decreased COX-2 expression and reduced paw swelling in rodent inflammatory models (Anderson et al, 1996). In murine osteoblasts, two anti-inflammatory cytokines, interleukin-4 and interleukin-13, inhibited COX-2 expression (Onoe et al, 1996). Analysis of human synovial tissue from patients with rheumatoid arthritis or traumatic injury showed increased COX-2 expression (Crofford et al, 1994).

Although COX-1 was not thought to be directly involved in inflammation, recent studies have demonstrated that both cyclooxygenase isoforms are detected in synovial cells from inflammatory joints (Crofford et al, 1994; Gilroy et al, 1998; Iniguez et al, 1998). In vitro analyses of cultured human synovial tissues show that macrophage, fibroblast, endothelial, and mononuclear inflammatory cells express both COX-1 and COX-2. In addition, in studies of COX-2 knockout mice, experimental challenges with inflammatory agents resulted in inflammatory responses that did not differ significantly from those in wild-type animals (Dinchuk et al, 1995; Morham et al, 1995). Thus, the presence of the COX-2 enzyme is not essential for inflammation to occur.

In contrast to findings in COX-2-deficient mice, inflammatory challenge in COX-1 knockout mice resulted in reduced inflammatory response (Langenbach et al, 1995), indicating that COX-2 is not the sole source of inflammatory prostanoids. These findings are contrary to established views that COX-1 is a constitutive, housekeeping enzyme responsible only for maintaining normal cell function and that COX-2 is inducible and solely responsible for inflammatory response. Rather,

the results of studies in cyclooxygenase knockout animals indicate that the physiologic roles of COX-1 and COX-2 require reassessment. Furthermore, if the two cyclooxygenase isoforms are involved in expressing inflammatory prostaglandins, agents that target both COX-1 and COX-2 may be more appropriate for anti-inflammatory therapy.

ROLE OF COX-2 IN THE GASTROINTESTINAL TRACT

ROLE OF COX-2 IN THE GASTROINTESTINAL TRACT

It is well established that many NSAIDs cause acute and chronic damage to the gastric mucosa (Wallace, 1997) and it has been postulated that this activity is related to cyclooxygenase inhibition. NSAID toxicity also extends to other areas of the GI tract, including the esophagus, small bowel, and colon (Gibson et al, 1992; Kaufman et al, 1996; Stamm et al, 1994). The pathogenesis of these other lesions is poorly understood, but presumably involves inhibition of prostaglandin synthesis by one or both cyclooxygenase enzymes. The effects of NSAIDs on the GI tract can be discussed, for convenience, under the categories of Gastric Lesions, Other Gastrointestinal Lesions, Healing of Lesions, and Effects on Epithelial Integrity.

GASTRIC LESIONS

With the identification of COX-1 and COX-2 isoenzymes, it was proposed that COX-1 was the isoform responsible for mediating gastric mucosal defense because inhibition of COX-1 led to gastric damage that was ameliorated by prostaglandin replacement. It was further proposed that COX-2 was not involved in gastric mucosal protection, and selective inhibition of COX-2 would spare gastric prostaglandin synthesis, reducing the likelihood for ulcerogenic effects. It is, of course, recognized that the cause of gastric lesion development with currently available NSAIDs is multifactorial and not completely understood.

Several recent studies have focused on the role of adaptive cytoprotection as a mechanism for preventing gastric injury. Chronic, low-grade injury of various kinds protects against acute injury. This adaptive cytoprotection may result from a local increase in protective prostaglandins.

OTHER GASTROINTESTINAL LESIONS

The cause of NSAID-induced ulceration in other areas of the GI tract is not well established. Prostaglandin replacement using misoprostol is not as effective in preventing (or treating) duodenal lesions as it is in preventing gastric lesions (Hawkey et al, 1998), suggesting that prostaglandin deficiency may not be as important in the initiation of duodenal ulcers. An important component related to development of duodenal ulcers in patients taking NSAIDs may be underlying *Helicobacter pylori* infection, with NSAIDs leading to an increased ulcer prevalence more by inhibiting healing than by causing ulcers de novo (see below). Finally, NSAIDs have been associated with strictures of the esophagus and colon (Davies, 1995; Eis et al, 1998), which could represent fibrosis secondary to delayed healing of lesions.

HEALING OF LESIONS

NSAIDs that nonselectively inhibit COX-1 and COX-2 have been shown to delay ulcer healing in animal models (Schmassmann, 1998; Schmassmann et al, 1995), and in man (Lancaster-Smith et al, 1991; Walan et al, 1989), and relevant effects on growth factor release have been demonstrated in cultured human gastric fibroblasts (Bamba et al, 1998). This is not surprising, in view of the close relationship between inflammation and wound healing (Stenson, 1997). COX-2 is intimately involved in wound healing, in the GI tract as well as in other tissues. However, it is not known to what extent the effect of nonselective NSAIDs on wound healing is mediated through inhibition of COX-2.

EFFECTS ON EPITHELIAL INTEGRITY

The GI tract constitutes an effective barrier against invasion by the large intestinal flora. The nature of the barrier is poorly understood, but it may involve fluid secretion, epithelial restitution, and other mechanisms. There is evidence to suggest involvement of prostaglandins in the function of this barrier. In addition, NSAIDs have been associated with disruption of the barrier and deleterious effects in patients with inflammatory bowel disease (Evans et al, 1997).

COX-2 EXPRESSION

The majority of cytoprotective prostaglandins in the GI tract are synthesized by constitutively expressed COX-1, which is found in essentially all GI tissues and is highly concentrated in the stomach, cecum, and colon (Kargman et al, 1996). However, a simplified theory whereby only COX-1 is responsible for production of cytoprotective prostaglandins can be called into question because COX-1 knockout mice did not demonstrate any abnormal GI physiology nor did they spontaneously develop gastric lesions, but did develop lesions when given oral indomethacin, albeit fewer than wild-type mice (Langenbach et al, 1995). This shows conclusively that inhibition of COX-1 is not necessary for NSAID-induced injury, and that other mechanisms must be involved. These could involve local effects (Somasundaram et al, 1997) or effects on COX-2. Although COX-2 in gastric mucosa is generally inducible, studies have shown that it also is constitutively expressed in the GI tract to some extent (Kargman et al, 1996). In rats, the highest concentration of constitutive COX-2 was found in the cecum and distal intestine. Furthermore, COX-2 has been shown to be constitutively expressed in human intestinal mucosa (Mahida et al, 1997).

Preclinical studies in mice and rats demonstrate a key role for COX-2 in maintaining mucosal integrity. In rats, COX-2 is expressed in gastric epithelial cells (Sasaki et al, 1998) and is important for proliferation (Sawaoka et al, 1997). In rat and mouse models of gastric mucosal lesion, COX-2 is expressed during acute stages of gastric mucosal injury (erosion, ulceration) and during ulcer healing (Kishimoto et al, 1998, 1997; Mizuno et al, 1997; Schmassmann et al, 1998). In one recent study in rats, COX-2 mRNA expression increased dramatically during the early phases of ischemia/reperfusion injury, then decreased as discrete ulceration occurred and was low during the ulcer healing stage (Kishimoto et al, 1998). However, because whole stomachs were used for the analysis, major elevations of COX-2 could have been present in the ulcer margins or ulcer base during the healing process.

Preclinical studies have shown that cytoprotection of the gastric mucosa in some situations (ethanol-induced damage after long-term endotoxin administration in rats; radiation injury) may relate, in part, to an inducible form of COX-1 (Cohn et al, 1997; Ferraz et al, 1997).

In one study, COX-2 was expressed in normal human gastric mucosa and human endothelial cells, and was significantly increased in the gastric ulcer margin (Tarnawski et al, 1997).

Spontaneous GI inflammation did not occur in COX-1 or COX-2 knockout mice, leading the authors of one study to question the proposed role of COX-1 in GI homeostasis (Morteau et al, 1997a). However, some COX-2 knockout mice developed peritonitis (Morham et al, 1995; Morteau et al, 1997a). In one recent study, indomethacin caused intestinal injury in COX-2 knockout mice, but not in normal controls (Wallace et al, 1998). The authors suggest that indomethacin administration may have led to dysregulation of inflammation in the COX-2 knockout mice, leading to tissue injury, whereas in normal mice the inflammation

would have resolved and any tissue damage would have healed. Furthermore, a study in rats demonstrated an elevation of COX-2 during inflammatory conditions, such as colitis, in the GI tract (Reuter et al, 1996). Increased susceptibility to experimentally induced colitis was seen in COX-2 knockout mice, but not in COX-1 knockout mice, suggesting that COX-2 may have more of a protective than inflammatory role in colitis (Morteau et al, 1997b).

In patients with ulcerative colitis, COX-2 has been shown to be upregulated in colonic apical epithelial cells (Singer et al, 1998). Biopsies from patients with active inflammatory bowel disease (ulcerative colitis or Crohn's disease) had a significantly ($P<.005$) higher expression of COX-2 than controls or patients with inactive disease; no difference in COX-1 expression was found (Hendel and Nielsen, 1997). In addition, COX-2 was shown to be upregulated in studies with human intestinal epithelial cells experimentally infected by invasive bacteria, as would occur-during enteric infection, causing rapidly increased intestinal fluid secretion as a protective mucosal mechanism (Eckmann et al, 1997). COX-1 expression was not affected by bacterial infection. The authors suggest that mucosal injury after infection with invasive bacteria could be exacerbated by selective inhibition of COX-2. Another recent study describes the role of endothelial-derived prostaglandin production produced by COX-2 in mediating secretion of fluid by intestinal epithelial cells (Blume et al, 1998), which contributes to questions regarding the protective role of COX-2 in prevention of mucosal injury.

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

Currently available preclinical data on COX-2 expression suggest that it is involved in mucosal repair. In animal models of chronic gastric erosion and ulceration, a highly selective COX-2 inhibitor impaired or delayed ulcer healing in mice (Mizuno et al, 1997) and in rats (Schmassmann et al, 1998; Shigeta et al, 1998; Tsuji et al, 1997). Stress-induced gastric ulcers were significantly increased with the use of a

selective COX-2 inhibitor in rats (San Miguel et al, 1998) and healing of stress-induced ulcers was significantly delayed in mice treated with selective COX-2 inhibitors (Ukawa et al, 1997).

Adaptive cytoprotection, thought to have a role in maintaining mucosal integrity, can be impaired by nonselectively inhibiting both COX-1 and COX-2 with indomethacin or by selectively inhibiting COX-2 (Brzozowski et al, 1998; Gretzer et al, 1998a). A selective COX-2 inhibitor also inhibits the protective effect of peptone in rat gastric mucosa and does not cause different effects than those seen with indomethacin (Ehrlich et al, 1997). In a rat model of mucosal resistance to ischemia/reperfusion injury, a selective COX-2 inhibitor significantly increased mucosal injury (Maricic et al, 1998). Other forms of adaptive cytoprotection do appear to be COX-1 mediated (Cohn, 1997). These findings suggest that the COX-2 isoenzyme is involved in generating prostaglandins necessary for gastric mucosal defense.

Highly selective COX-2 inhibitors have been shown to exacerbate experimental colitis in rats, leading to death caused by colonic perforation in many of the animals (Reuter et al, 1996).

Interestingly, results of a recent study demonstrate that the lowest doses of two selective COX-2 inhibitors necessary for statistically significant reduction of carrageenan-induced rat paw edema were high enough to also significantly inhibit COX-1 activity (Wallace et al, 1998). At the doses necessary to significantly reduce prostaglandin synthesis in the rat paw, gastric prostaglandin synthesis was also significantly inhibited and the selective COX-2 inhibitors caused hemorrhagic erosions ($P<.05$ versus vehicle). These results were confirmed by other researchers who determined that doses of a selective COX-2 inhibitor necessary to inhibit prostanoid production in human bursal tissue also inhibit COX-1 (Gretzer et al, 1998b).

USE OF SELECTIVE COX-2 INHIBITORS IN MAN

Limited human data are available to address potential concerns based on animal studies with selective COX-2 inhibitors. Studies are available demonstrating that a selective COX-2 inhibitor (MK-0966) did not increase intestinal permeability (Bjarnason et al, 1998) or fecal blood loss (Hunt et al, 1998) to any greater degree than placebo, although the clinical relevance of these data are unclear. Short-term (1- to 2-week) endoscopic studies in healthy volunteers have shown no or minimal GI damage based on endoscopic score or erosion/ulcer development with MK-0966 (Lanza et al, 1997a), celecoxib (Lanza et al, 1997b), or nimesulide (Shah et al, 1998) that was similar to placebo and significantly less than with ibuprofen or naproxen. However, short-term endoscopic data have not been shown to be a reliable indicator of the development of potentially serious GI complications. Nimesulide was evaluated endoscopically for 1 week in 30 patients with dyspepsia; patients with a history of ulcer, complication, or severe dyspepsia were excluded (Marini and Spotti, 1993). Based on endoscopic score, the effects of nimesulide were shown to be similar to those of placebo.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE GASTROINTESTINAL TRACT

In the GI tract, it is apparent that COX-2 has a more expanded role than originally believed and is important for several normal mucosal-protective mechanisms. Adaptive cytoprotection may prove to be a very important phenomenon in the stomach, particularly if it results from chronic *H pylori* infection. The extent to which it is dependent on COX-1 or COX-2 needs further elucidation. However, if COX-2 is shown to have an important role, the possible effects of COX-2 inhibition by highly selective inhibitors will need further evaluation.

Although highly selective COX-2 inhibitors may be less likely than other NSAIDs to *cause* initial gastric mucosal lesions, it is possible that they will delay or impair ulcer healing, either in the stomach or elsewhere. This is important because most NSAID-induced ulcers heal spontaneously, and it is the failure to heal, with progression to penetration through the muscularis mucosae, that leads to most complications.

Finally, delayed or dysregulated healing of lesions in other parts of the GI tract might be responsible for NSAID-induced fibrosis and stricture formation (eg, in the esophagus or colon). (Refer also to discussions of fibrosis in the cardiac and pulmonary sections of this document.) NSAIDs, through effects on healing or other mechanisms, could compromise the colonic barrier to infection, with consequent sepsis or peritonitis; this might be most consequential in patients suffering from inflammatory bowel disease or in patients with ascites. If these effects of NSAIDs are mediated preferentially by inhibition of COX-2, they may constitute important concerns about the use of highly selective COX-2 inhibitors. Some of these questions regarding the GI safety of selective COX-2 inhibitors have been raised previously (Stenson, 1997; Yeomans et al, 1998).

ROLE OF COX-2 IN THE RESPIRATORY TRACT

ROLE OF COX-2 IN THE KIDNEY

The kidney is a significant source of cyclooxygenase-mediated prostaglandin synthesis as well as a target organ for prostaglandin effects, particularly with regard to maintenance of renal blood flow in the compromised kidney. The use of NSAIDs in normal, healthy individuals is not associated with an untoward risk of adverse renal effects. However, patients with volume-depleted states, congestive heart failure, advanced age, or conditions associated with preexisting renal insufficiency are at risk for NSAID-induced adverse renal events, such as edema, hyperkalemia, acute renal failure, or nephrotic syndrome with interstitial nephritis (Whelton and Hamilton, 1991). Acute deterioration of renal function in high-risk patients is most concerning and occurs with disruption of the delicate balance between pressor mechanisms and prostaglandin-associated vasodilation. Inhibition of prostaglandins by NSAIDs allows for unopposed vasoconstriction, potentially leading to serious renal sequelae. Chronic, long-term use of NSAIDs has been associated with papillary necrosis in some rare situations. The effects of NSAIDs on salt and water homeostasis also may be responsible for the increased risk of hospitalization due to congestive heart failure (Heerdink et al, 1998) and interactions with antihypertensive medications (Houston et al, 1995; Johnson et al, 1993; Pope et al, 1993).

Historically, it was believed that COX-1 was expressed constitutively in the kidney for purposes of maintaining renal homeostasis. COX-2 was thought to be an inducible isoform that was normally absent, but would rapidly be expressed to meet a specific physiologic challenge, such as inflammation or compromised renal blood flow (Morham et al, 1995; Vane et al, 1998). However, emerging data demonstrate the role of COX-2 in normal renal development, the constitutive expression of COX-2 in the kidney, and the renal effects of COX-2 inhibition (Schneider and Stahl, 1998), all of which may have implications for the use of selective COX-2 inhibitors

in patients with compromised renal function, those taking antihypertensive medication, or in those with borderline cardiovascular compensation.

COX-2 EXPRESSION

COX-2 plays a role in the normal development of the kidney. High levels of COX-2 have been found in the developing nephrons and bladders of neonatal mice, underscoring the involvement of COX-2 in nephrogenesis (Park et al, 1997; Zhang et al, 1997). Several studies have demonstrated that COX-2 knockout mice exhibit severe congenital renal abnormalities (Dinchuk et al, 1995; Morham et al, 1995; Norwood, 1998). Kidneys of neonatal COX-2 knockout mice are significantly underdeveloped, with a disproportionately small number of functional nephrons and a large quantity of undeveloped mesenchymal tissue. In contrast, neonatal COX-1 knockout mice did not exhibit renal abnormalities, indicating that this isoform is not essential to normal renal growth and development (Langenbach et al, 1995). Adult COX-2 knockout mice exhibit reduced numbers of functioning nephrons and severe nephropathy, including glomerular sclerosis and tubulointerstitial injury (Dinchuk et al, 1995; Morham et al, 1995).

The constitutive expression of both COX-1 and COX-2 has been identified in renal tissues of animal models and man. In normal, unchallenged rats, COX-2 is expressed constitutively in the macula densa of the juxtaglomerular apparatus, in bordering epithelial cells of the cortical thick ascending limb of Henle, and in papillary interstitial cells. COX-2 is not found in renal arterioles, glomeruli, or collecting ducts in the rat. COX-1 is also expressed constitutively, but in distinctly different locations, namely the medullary collecting ducts and medullary interstitial cells (Harris et al, 1994). In rabbits, COX-2 is expressed constitutively in the bladder and in the outer medullary interstitial cells and cortical macula densa of the kidney. COX-1 is not found in the medullary interstitial cells of rabbits (Guan et al, 1997).

COX-2 is also expressed constitutively in adult and fetal human kidneys. In a study of adult human kidneys, COX-2 was located in glomerular podocytes and in endothelial and smooth muscle cells of renal arteries and veins, but not in glomerular endothelia. COX-1 was located in collecting duct cells, cortical and medullary interstitial cells, and endothelial cells of the afferent arteriole. In human fetal kidneys, COX-2 was found in arterial and venous endothelia and smooth muscles and in mature glomeruli. COX-1 was found in the collecting duct cells and podocytes of fetal human kidneys, suggesting a role in nephrogenesis (Kömhoff et al, 1997). The authors of this study conclude that the location of COX-2 suggests this isoform is involved in maintenance of renal hemodynamics and that development of a completely renal-sparing COX-2 inhibitor is unlikely.

Preclinical data demonstrate the role of COX-2 in maintaining normal sodium and water balance. Certain experimental, physiologic challenges mimicking clinical disease (eg, intravascular volume expansion or contraction) result in increased production of COX-2 in the kidney (Harris et al, 1994; Yang et al, 1998). For example, mice fed a low-sodium diet (ie, volume-contraction) exhibit markedly increased expression of COX-2 that is threefold greater than basal levels (Harris et al, 1994). Chronic volume expansion had no effect on basal expression of COX-2 in one murine study (Harris et al, 1994), but resulted in increased levels in another (Yang et al, 1998). Surgically induced renovascular hypertension in mice increases levels of COX-2 in the macula densa that parallel increases in renin levels, indicating a role for COX-2 in renin release associated with altered renal perfusion (Hartner et al, 1998).

The location of COX-2 in the kidney may dictate specific functions. COX-2 found in the renal medulla has been implicated in the control of sodium and water excretion in volume-overload states. In addition, it has been suggested that cortical COX-2 mediates glomerular circulation in volume-depleted states (Yang et al, 1998).

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

In one study, dogs received intravenous doses of indomethacin, 6-MNA (the active metabolite of nabumetone), or a selective COX-2 inhibitor (Brooks et al, 1998). The selective COX-2 inhibitor and indomethacin caused significant, dose-related reductions in urine flow, sodium excretion, renal plasma flow, and glomerular filtration rate. 6-MNA had no measurable effect on these or other parameters of renal function. In another study in mice, the normal renal response in animals fed a low-sodium diet (ie, increased renal renin release) was blocked by a selective COX-2 inhibitor (Harding et al, 1997), suggesting that COX-2 is a requirement for renin release by the kidney.

USE OF SELECTIVE COX-2 INHIBITORS IN MAN

The renal effects of two selective COX-2 inhibitors, nimesulide and flosulide, have been measured in short-term studies in young, healthy subjects (Brunel et al, 1995; Steinhäuslin et al, 1993) and the renal effects of celecoxib were recently evaluated in healthy, salt-depleted subjects in a short-term study (Rossat et al, 1998). Nimesulide has been withdrawn from the market, and clinical testing of flosulide has been halted (Donnelly and Hawkey, 1997). Administration of flosulide (25 mg twice daily for 9 days) or nimesulide (200 mg twice daily for 10 days) resulted in significant blunting of compensatory increases in plasma renin and aldosterone concentrations compared with placebo during orthostatic challenge and sodium depletion with furosemide (Brunel et al, 1995; Steinhäuslin et al, 1993). These observations, made during short-term administration to young, healthy volunteers, support the notion that selective inhibition of COX-2 is not sufficient to protect against renal toxicity during NSAID use, particularly in patients at risk for renal dysfunction.

A recent study evaluated the renal effects of a selective COX-2 inhibitor, celecoxib (200 or 400 mg/d), compared with placebo or naproxen (500 mg twice daily), for 8 days in 40 healthy volunteers on a low-sodium diet (Rossat et al, 1998). Peak changes in renal hemodynamics occurred at 1 hour on day 1, when 400 mg/d of celecoxib significantly ($P<.05$) decreased glomerular filtration rate and renal plasma flow when compared with baseline. Significant reductions in sodium excretion also occurred at 2 hours on day 1 with either dose of celecoxib versus placebo ($P<.01$) and in potassium and lithium excretion with the higher celecoxib dose ($P<.01$ versus placebo). The authors indicate in their conclusions that COX-2 has a major role in maintaining sodium balance and renal vascular tone in salt-restricted individuals.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE KIDNEY

COX-2, like COX-1, is expressed constitutively in the kidney and mediates sodium and water balance, intravascular volume, and blood pressure. Because many NSAIDs inhibit both isozymes, it is not clear whether the known effects of NSAIDs on renal function are due to inhibition of COX-1, inhibition of COX-2, or a combination. COX-2 appears to be involved in renal homeostasis to a greater degree than previously believed, therefore, the concept that selective COX-2 inhibitors are renal-sparing requires reconsideration. The effects of these agents will need to be assessed in patients in whom COX-2 is upregulated, including patients with compromised renal function, patients taking an angiotensin-converting enzyme (ACE) inhibitor and diuretics for hypertension, and patients with volume overload and borderline cardiac decompensation.

ROLE OF COX-2 IN FERTILITY AND REPRODUCTION

ROLE OF COX-2 IN FERTILITY AND REPRODUCTION

Prostaglandins play a key role in ovulation and pregnancy, and inhibition of prostaglandin synthesis blocks ovulation in several species. Following fertilization, development of the embryo during the blastocyst stage and synchronized differentiation of the uterus depend on the coordinated effects of estrogen, progesterone, and vasoactive prostaglandins. COX-1 and COX-2 are expressed in uterine tissues at various times during pregnancy (Vane et al, 1998). Because the presence of COX-2 in the uterus has only recently been established, the roles of COX-1 and COX-2 in reproductive functions remain to be determined. Many prostaglandin effects initially thought to be associated with constitutively expressed COX-1 may actually be attributed to COX-2. Indeed, one author suggested that ovulation and implantation are processes that may be considered analogous to a proinflammatory response (Lim et al, 1997).

COX-2 EXPRESSION

During pregnancy, COX-2 is highly involved in a number of crucial events. Animal studies indicate that COX-2 expression is essential for ovulation, fertilization, implantation, and decidualization (Lim et al, 1997; Song et al, 1998). Remarkably, COX-2 expression appears to be precisely timed with respect to ovulation, although timing varies from species to species (Boerboom and Sirois, 1998; Liu et al, 1997; Richards, 1997; Sirois, 1994; Sirois and Doré, 1997). COX-2 is induced in rat preovulatory follicles by luteinizing hormone and human chorionic gonadotropin (Sirois and Richards, 1992). Studies in bovine endometrial cells showed that oxytocin stimulated prostaglandin $F_{2\alpha}$ production, and that this correlated with upregulation of COX-2 gene expression during luteolysis (Asselin et al, 1997; Xiao et al, 1998). COX-2 levels increase significantly before and after labor, and prostaglandins produced by COX-2 may be necessary for delivery of the fetus (Gibb

and Sun, 1996; Slater et al, 1998). In bovine uterine tissues, COX-2 is the predominant isoform and concentrations increase during late pregnancy (Fuchs et al, 1998). In cultured cells, significant levels of COX-1 and COX-2 also are expressed in human umbilical endothelial cells and smooth muscle cells, although minute amounts of the two isoenzymes are found in biopsies from human umbilical arteries and veins (Öst et al, 1998).

Reproductive data elucidated from COX-2 knockout mice are particularly interesting and suggest that COX-2 has an essential role in maintaining fertility and is necessary during each stage of pregnancy (Lim et al, 1997; Majerus, 1998). In COX-2 knockout mice, females lacking COX-2 are infertile, having defective ovulation and failure of fertilization (Dinchuk et al, 1995; Lim et al, 1997). Although ovarian follicular development appears normal in COX-2 knockout mice, ovaries are small because of the absence of corpora lutea (Dinchuk et al, 1995). Female COX-2 knockout mice produce half as many ova per cycle as wild-type mice, and none of the ova was fertilized during mating attempts (Lim et al, 1997). COX-1 knockout mice are fertile, although the homozygous matings tend to result in stillborn normal-size litters. The cause for litter death in COX-1 knockout mice remains undetermined (Langenbach et al, 1995).

In addition to impaired oocyte maturation, COX-2 knockout mice have failed decidualization of the uterus and defective implantation of blastocysts (Lim et al, 1997; Majerus, 1998). Blastocyst implantation was noted in only 1% of COX-2 knockout mice compared with 50% of wild-type mice (Lim et al, 1997). During the implantation period, COX-2 also is highly expressed in the embryo. In ovine embryos, COX-1 is absent, whereas COX-2 is expressed during days 8 to 17 following fertilization, suggesting that COX-2 has an early role in embryonic development and interaction with the uterus (Charpigny et al, 1997).

Decidualization of the uterus also is impaired in COX-2 knockout mice. In endometrial stromal cells isolated from rats that have been sensitized for decidualization, both COX-1 and COX-2 are produced in response to epidermal growth factor (Bany and Kennedy, 1997). However, COX-2 knockout mice that are artificially induced to a pseudopregnant stage via oil infusion into the uterus fail to develop increased uterine weight, indicating that decidualization does not occur in these mice (Lim et al, 1997). Thus, implantation and decidualization are impaired in the absence of COX-2.

Prostaglandins produced in response to COX-2 also play an important role in parturition. In human amnion at term, COX-2 expression increases after the onset of labor, and expression of COX-2 mRNA is 100-fold greater than that of COX-1 mRNA (Slater et al, 1995, 1994). Additionally, COX-2 expression in the amnion increases twofold in laboring women compared with nonlaboring women who deliver via cesarean section, suggesting that COX-2 is necessary for spontaneous labor (Fuentes et al, 1996). COX-2 expression also increases in chorion-decidual cells with the onset of labor (Slater et al, 1998). Both COX-1 and COX-2 are expressed in the myometria during pregnancy. During term pregnancy, COX-2 expression is greater than COX-1 expression in the myometrium (Zuo et al, 1994). These findings suggest that COX-2 is responsible for prostaglandin production during labor and that selective inhibition of the COX-2 isoenzyme may delay spontaneous labor in pregnant women.

In the human placenta at term, COX-2 is the predominant cyclooxygenase isoform and COX-1 is detected only in negligible quantities (Macchia et al, 1997). Using a rat model for preterm labor, COX-2 expression was rapidly stimulated in the placenta in response to lipopolysaccharide (Swaisgood et al, 1997). Thus, it has been suggested that COX-2 is responsible for placental production of prostaglandin E_2, which is essential for maturation and maintenance of the placenta. This may correlate with the antiapoptotic and growth-promoting properties of prostaglandins

produced by the COX-2 isoenzyme. In the human placental bed, COX-1 expression is increased in preeclampsia, whereas COX-2 expression remains the same as in normal pregnancies (Wetzka et al, 1997). Both cyclooxygenase isoenzymes are increased in preeclamptic umbilical cord vessels (Beharry et al, 1998).

The role of prostaglandins in male reproductive functions remains largely unknown. There is evidence that COX-2-derived prostaglandins may be involved in erection. In rats, constitutively expressed COX-2 is the predominant isoform in the male reproductive system and is primarily located in the epithelium of the distal vas deferens (McKanna et al, 1998). It has been postulated that prostaglandins from the vas deferens are largely responsible for erectile function.

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

COX-1 knockout mice have normal blastocyst implantation. However, treatment with high doses of a selective COX-2 inhibitor resulted in failure of implantation (Lim et al, 1997). Similar effects were noted when wild-type mice were treated with high-dose, selective COX-2 inhibitors.

USE OF SELECTIVE COX-2 INHIBITORS IN MAN

Although data on potential reproductive effects of selective COX-2 inhibitors have not been published, there is a report of infertility, associated with luteinized, unruptured follicles, in three women who received NSAIDs for arthritis (Smith et al, 1996). Ovulation occurred in each patient when the NSAIDs were discontinued. In view of the important role of COX-2 in ovulation, this occurrence may have been related to inhibition of COX-2.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN REPRODUCTION AND FERTILITY

Preclinical data from COX-2 knockout mice and studies with selective COX-2 inhibitors in mice suggest that expression of COX-2 is an essential feature of ovulation and pregnancy and that complete inhibition of COX-2 may prevent normal ovulation. Furthermore, these findings suggest that the case reports of infertility in humans may be related to COX-2 inhibition. Thus, it may be speculated that selective COX-2 inhibition may produce unwanted effects on fertility.

In addition, data from COX-2 knockout mice show that COX-2 expression is necessary for each step of pregnancy (eg, ovulation, fertilization, implantation, and decidualization). Prostaglandins generated by COX-2 are necessary for maintaining pregnancy in several species. Therefore, selective inhibition of COX-2 may interfere with pregnancy in several ways (Majerus, 1998). Agents that selectively inhibit COX-2 probably will require the same precautions as other NSAIDs with respect to use during pregnancy.

Finally, irrespective of effects on pregnancy, the effects of selective COX-2 inhibition on corpus luteum development in nonpregnant women may result in long-term hormonal changes that may affect estrogen-sensitive tissues, such as uterus, breast, and bone.

ROLE OF COX-2 IN THE CENTRAL NERVOUS SYSTEM

ROLE OF COX-2 IN THE CENTRAL NERVOUS SYSTEM

It is unclear whether NSAID-induced central nervous system effects, such as headache, dizziness, drowsiness, and confusion (Insel, 1990; Kaplan and Swain, 1993) are directly related to cyclooxygenase inhibition. Although the cellular source of prostaglandins in the brain is uncertain, prostaglandins are implicated in several brain functions, including control of sleep-wake cycles, temperature regulation, and pituitary hormone production (Caggiano et al, 1996; Kaufmann et al, 1997). In certain regions of the brain, COX-2 is expressed by neurons, and expression increases during neuronal activity. The cyclooxygenase isoenzymes may have a role in neurologic disorders, cerebrovascular disease, migraines, neuronal death following ischemia, and in Alzheimer's disease, although the precise roles of the two isoenzymes remain to be determined (Kaufmann et al, 1997; Osuka et al, 1998; Tocco et al, 1997).

COX-2 EXPRESSION

The animal brain, and probably the human brain as well, contains high concentrations of prostaglandins D_2 and E_2, which may be involved in sleep regulation (Hayaishi, 1991). In animal models, COX-1 is found mainly in the forebrain, where prostaglandins may be involved in sensory processing (Yamagata et al, 1993). The human brain contains equal amounts of mRNA for COX-1 and COX-2, and both isoenzymes are expressed constitutively in the brain and spinal cord (O'Neill and Ford-Hutchinson, 1993; Resnick et al, 1998; Vane et al, 1998).

Although COX-1 is constitutively expressed in most tissues, there is evidence that COX-1 expression may be induced in rat cerebral cortex following ischemia (Holtz et al, 1996). COX-2 also is induced following cerebral ischemia and is associated with a significant increase in prostaglandin E_2 production (Collaco-Moraes et al, 1996;

Nogawa et al, 1997). Data from animal studies suggest that COX-2 may be involved in the mechanisms of delayed neuronal death following a cerebral infarct (Iadecola and Ross, 1998; Nogawa et al, 1997; Osuka et al, 1998), and similar findings have been observed in the infarcted human brain (Sairanen et al, 1998). COX-2 also is induced in the hippocampus during intense nerve stimulation (eg, seizures) and in the cerebral cortex during acute stress, suggesting that COX-2 is upregulated during neuronal activity (Marcheselli and Bazan, 1996; McCown et al, 1997; Yamagata et al, 1993). Following brief, noninjurious electrical stimulation in rat brains, COX-2 levels remained elevated for weeks and may have sustained effects on brain function (Caggiano et al, 1996).

COX-2 expression is induced in the brain by the presence of pyrogenic substances, such as interleukin-1 and tumor necrosis factor (Cao et al, 1998, 1996). In rodents, COX-2 induced by interleukin-1 is responsible for the production of fever-producing prostaglandins (Cao et al, 1996). COX-2 clearly is involved in the febrile response (Cao et al, 1998; Matsumura et al, 1997). Using a murine model of infection, systemic injection of lipopolysaccharide led to robust expression of COX-2 in perivascular cells and the choroid plexus (Breder, 1997).

Aside from pathologic expression, low levels of COX-2 mRNA are detected in the animal brain under basal conditions, particularly in neonates (Breder et al, 1995; Parfenova et al, 1997; Yamagata et al, 1993). In the newborn pig, both cyclooxygenase isoenzymes are constitutively expressed in cerebral microvessels and microvascular endothelium (Parfenova et al, 1997). In the rat brain, COX-2 is constitutively expressed in the cortex, hippocampus, hypothalamus, and spinal cord (Breder et al, 1995; Breder and Saper, 1996). In rat cerebral cortex, COX-2 is located in the discrete dendritic branches and dendritic spines of excitatory pyramidal neurons. These findings suggest that COX-2 has a direct effect on postsynaptic signaling of excitatory neurons (Kaufmann et al, 1996). COX-2 expression is noted in the specific corticallaminae and subcortical nuclei. Within

the amygdala, COX-2 is observed in the caudal and posterior of the deep and cortical nuclei, and in the diencephalon COX-2 appears in the paraventricular nucleus of the hypothalamus and in the anteroventral region surrounding the third ventricle. In the brainstem of the rat, COX-2 appears in the dorsal raphe nucleus, the nucleus of the brachium of the inferior colliculus, and in the region of the subcoeruleus (Breder et al, 1995). The highest basal levels of COX-2 in the rat appear in the hippocampus, the pyramidal cells of the piriform cortex, neocortex, and amygdala complex (Breder et al, 1995; Yamagata et al, 1993). Lower levels have been found in the caudate-putamen, thalamus, hypothalamus, superficial layers of the neocortex, striatum, and preoptic area (Cao et al, 1995; Yamagata et al, 1993). Although the physiologic significance of constitutively expressed COX-2 is not known, varying levels of COX-2 expression in the brain suggest that it may have a variety of different functions under normal physiologic conditions.

Unlike COX-1, COX-2 is not diffusely located within the rat brain. Rather, it is discretely organized and may be localized in specific membrane compartments (Breder et al, 1995; Kaufmann et al, 1997). The location and distribution of COX-2 in rodent brains indicate that COX-2 may be involved in processing visceral and sensory input. In addition, COX-2 may play a role in the generation of autonomic, endocrine, and behavioral responses (Breder et al, 1995).

COX-2 also is expressed in the spinal cord of rats and may be involved in spinal nociception (Beiche et al, 1996; Hay et al, 1997; Ichitani et al, 1997; Willingale et al, 1997; Yamamoto and Nozaki-Taguchi, 1996). Studies using the rat have shown that COX-1 and COX-2 mRNA are expressed constitutively in the spinal cord and that COX-2 is the predominant isoform (Beiche et al, 1996; Willingale et al, 1997). These studies indicate that both cyclooxygenase isoforms may play a role in spinal nociception.

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

In newborn pigs, prostaglandin receptor densities were increased and prostaglandin E_2 and $F_{2\alpha}$ levels were significantly reduced by ibuprofen and selective COX-2 inhibitors, but were not affected by a COX-1-specific inhibitor. Treatment with ibuprofen and selective COX-2 inhibitors also increased blood pressure in the cerebral cortex of newborns (Li et al, 1997). It was postulated that these prostaglandins are important in maintaining cerebral blood flow in the newborn brain (Peri et al, 1995). In newborn pig cerebral microvasculature, selective COX-2 inhibition significantly decreased prostanoid synthesis and may have a substantial effect on newborn cerebral circulation (Parfenova et al, 1997).

Using the formalin test in rats as a model for pain, one study noted that a nonselective cyclooxygenase inhibitor, ibuprofen, effectively blocked prostaglandin E_2 release and decreased hyperalgesic response. Notably, administration of two different selective COX-2 inhibitors was ineffective, suggesting that in acute situations, spinal COX-1, but not COX-2, is responsible for synthesis of prostaglandin E_2 and nociception (Dirig et al, 1997).

In vitro studies have found that some NSAIDs may exhibit proinflammatory effects, such as generation of superoxide in neutrophil cells (Twomey and Dale, 1992). One analysis of rat mesangial cells found that treatment with a selective COX-2 inhibitor induced COX-2 mRNA (although the production of COX-2 metabolites was blocked) and significantly increased the level of inducible nitric oxide synthase produced by the cells. The authors of this study postulated that proinflammatory actions may account for unexplained adverse effects associated with selective COX-2 inhibition, although the effects may be restricted to the rat model. The clinical implications of these findings remain to be determined (Klein et al, 1998).

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE CENTRAL NERVOUS SYSTEM

Based on localization of COX-2 in the brain of animal models, particularly in newborns, it is possible that inhibition of COX-2 may be associated with gross sensory or behavioral changes. However, the role of COX-2 and the functional distinction between the two cyclooxygenase isoforms in the brain still remains unclear. Therefore, the effects of selective COX-2 inhibition in the human brain are unknown. Evidence from rat mesangial cells showed that selective COX-2 inhibition induces nitric oxide synthase and suggests that proinflammatory effects may be associated with adverse effects. The ability of COX-2 inhibitors to cross the blood-brain barrier remains to be investigated.

ROLE OF COX-2 IN THE CARDIOVASCULAR SYSTEM

ROLE OF COX-2 IN THE CARDIOVASCULAR SYSTEM

Prostaglandins have diverse roles in the heart and vasculature, including proinflammatory effects and vasodilation. COX-2 catalyzes the conversion of prostaglandin precursors to prostacyclin, a key vasoactive substance involved in regulation of vascular tone and perfusion. The adverse-effect profile of NSAIDs in patients with compromised cardiac function can include increased systemic vascular resistance and reductions in cardiac output, renal blood flow, and glomerular filtration (Dzau et al, 1984; Townend et al, 1995; Vane et al, 1998). In addition, prostaglandins produced by COX-2 may have a role in promoting tissue repair following injury.

COX-2 EXPRESSION

COX-2 is generally believed to be an inducible enzyme in cardiac and vascular tissues (Holmes et al, 1997; Rimarachin et al, 1994; Wong et al, 1998), although one recent in vitro study suggests that COX-2 may be constitutively expressed in rat aorta (Connolly et al, 1998). However, COX-2 knockout mice exhibit diffuse myocardial fibrosis in both ventricles and mild cardiac myofiber dropout, indicating that COX-2 deficiency may be implicated in cardiomyopathy (Dinchuk et al, 1995) and that COX-2 itself may be cardioprotective (Wu, 1998).

In a study in humans, COX-2 was not identified in hearts from healthy controls, but was identified in the myocytes and inflammatory cells of infarcted myocardial tissue in patients with heart failure secondary to sepsis or ischemic heart disease (Wong et al, 1998). In patients with heart failure secondary to dilated cardiomyopathy, COX-2 was found in fibrotic cardiac tissue, but not in myocytes or inflammatory cells.

In rabbit aorta, high-density lipoprotein (HDL) has been demonstrated to induce COX-2 expression (and increase levels of the vasodilator, prostacyclin) in smooth muscle cells (Viñals et al, 1997).

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

The effects of a selective COX-2 inhibitor and a nonselective COX-1/COX-2 inhibitor (indomethacin) on vascular contractility of endothelium-denuded aorta were assessed in a murine model (Connolly et al, 1998). Both agents blocked α-agonist-induced vasoconstriction, presumably due to inhibition of COX-2. The authors speculated that COX-2 was produced constitutively in rat aorta because the experimental procedures were undertaken before the extracted tissue would have been able to induce and express the isoform.

In another preclinical study, dogs were given intravenous doses of indomethacin, 6-MNA, or a selective COX-2 inhibitor (Brooks et al, 1998). Neither 6-MNA nor indomethacin altered baseline heart rate or blood pressure, but the selective COX-2 inhibitor caused significant bradycardia (-24 bpm ± 5%) without changes in blood pressure.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE CARDIOVASCULAR SYSTEM

Available data on COX-2 expression in infarcts and cardiomyopathy suggest that COX-2 has a role in both inflammation and repair. Complete suppression of COX-2, as in knockout mice, may have further implications than inhibiting inflammation and may, in fact, inhibit repair. This may lead to excessive fibrosis and deleterious consequences in patients with cardiac or vascular injury.

COX-2 also appears to be involved in the control of vascular tone, participating in HDL-induced production of vasodilatory prostaglandins and α-agonist-induced vasoconstriction. The consequences of inhibiting these effects remain to be determined, but could have long-term implications.

ROLE OF COX-2 IN

THE KIDNEY

ROLE OF COX-2 IN THE RESPIRATORY TRACT

The use of NSAIDs in asthmatic inflammatory conditions is controversial because inhibition of cyclooxygenase isoenzymes may increase production of leukotrienes and enhance airway responsiveness, worsening asthmatic symptoms (Szczeklik, 1983). COX-1 and COX-2 both catalyze the conversion of arachidonic acid to prostaglandin, and inhibition of either enzyme may increase leukotriene production. In addition to these effects on arachidonic acid metabolism, recent findings have demonstrated that COX-2 is involved in a variety of physiologic and regulatory processes in the pulmonary system.

COX-2 EXPRESSION

Although COX-2 has a role in some noninfectious inflammatory processes in the respiratory tract (Fernández-Morata et al, 1997; Kato et al, 1998; Vadas et al, 1996), it also may have distinct regulatory functions under physiologic conditions. In animals, constitutively expressed COX-2 has been isolated from the lung (Brannon et al, 1998; Charette et al, 1995; Ermert et al, 1998). In rats, both cyclooxygenase isoforms are detected in the lungs (Ermert et al, 1998). COX-2 is noted primarily in macrophage and mast cells, smooth muscle cells of partially muscular vessels, large veins of the hilum, and bronchial epithelial cells. Extensive localization of COX-2 in the rat lung suggests that it has a physiologic, as well as an inflammatory, role in the respiratory tract. In the guinea pig, COX-2 expression is responsible for maintaining intrinsic tone in the trachea (Charette et al, 1995).

In fetal and newborn sheep lungs, COX-2 mRNA expression increased during the fetal to 1-week-old period (Brannon et al, 1998). However, COX-2 protein was not detected in the developing ovine lung. There is no evidence that COX-2 knockout mice exhibit pulmonary pathology (Dinchuk et al, 1995).

In the cultured human airway smooth muscle cell, COX-2 is not expressed under control conditions. However, COX-2 expression is stimulated by proinflammatory cytokines and bradykinin, and expression is inhibited by dexamethasone and both selective and nonselective COX-2 inhibitors (Belvisi et al, 1997; Pang and Knox, 1997a, 1997b; Vigano et al, 1997).

High levels of COX-2 mRNA are present in the normal human lung, whereas levels of COX-1 are approximately twofold lower (O'Neill and Ford-Hutchinson, 1993). In patients with stable asthma and chronic bronchitis, both cyclooxygenase isoforms are found in respiratory epithelium, but COX-2 is not upregulated (Demoly et al, 1997). In upper respiratory mucosa of patients with chronic allergic rhinitis and sinusitis and in control patients, COX-1 and COX-2 are expressed in the epithelium and neither enzyme is upregulated during this noninfectious inflammation (Demoly et al, 1998). Both cyclooxygenase isozymes are expressed in nonstimulated epithelial cells isolated from nasal polyps (Kowalski et al, 1997). Therefore, constitutive expression of COX-2 in the lungs, and its failure to increase in the presence of noninfectious inflammation, suggests a more basic, homeostatic role, rather than one restricted to supporting inflammation.

In one interesting study, lung fibroblasts from patients with idiopathic pulmonary fibrosis did not respond to inflammatory stimuli (eg, PMA, lipopolysaccharide, IL-1) with increased COX-2 expression or activity (Wilborn et al, 1995). Because one of the effects of prostaglandin E_2 is to inhibit fibroblast proliferation and collagen synthesis, the authors postulated that the inability of these patients to upregulate COX-2 and increase prostaglandin production might inhibit reparative processes, allowing more opportunity for fibroblasts to lay down connective tissue and promoting the development of pulmonary fibrosis. They further suggested that "potential detrimental consequences might result from pharmacologic inhibition of COX-2, at least during the reparative phases of inflammatory injury in the lung" (Wilborn et al, 1995).

ROLE OF COX-2 IN THE PANCREAS

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

In isolated guinea pig trachea, a selective COX-2 inhibitor and indomethacin were used to evaluate effects on intrinsic tone (Charette et al, 1995). Both agents reversed intrinsic tone, with the selective COX-2 inhibitor exhibiting greater effect, implying that COX-2 is responsible for maintaining intrinsic tone in the trachea.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE RESPIRATORY TRACT

Constitutive expression of COX-1 and COX-2 in the human lung clearly suggests that there is a role for these isoenzymes in maintaining normal, homeostatic functions. Furthermore, in patients with asthma or noninfectious rhinitis and sinusitis, COX-2 expression is not upregulated, as would be expected in inflammatory conditions, providing further support for a noninflammatory role for this isozyme. The consequences of inhibiting these unknown functions remain to be determined. The observation that patients with idiopathic pulmonary fibrosis are unable to induce COX-2 expression in the lung raises the question of whether selective inhibition of COX-2 might inhibit the reparative phases of inflammatory injury in the lung, or otherwise contribute to the development of fibrosis.

ROLE OF COX-2 IN THE PANCREAS

Both COX-1 and COX-2 have been shown to be expressed in acinus cells of the pancreas in rats, both during normal conditions and during pancreatitis (Zabel-Langhennig et al, 1998). However, in pancreatic islet beta cells from hamsters, rats, and humans, COX-2 was recently shown to be constitutively expressed whereas minimal, if any, COX-1 is expressed (Sorli et al, 1998). COX-2 was also predominant during interleukin-1-stimulated conditions. The clinical relevance of these data, if any, to use of selective COX-2 inhibitors is unknown.

LITERATURE SEARCHES CONDUCTED TO DEVELOP THIS DOCUMENT

LITERATURE SEARCHES CONDUCTED TO DEVELOP THIS DOCUMENT

The literature searches completed to develop this document were performed by Grace Johnson, PharmD, who is an Editor with Scientific Therapeutics Information, Inc, a medical communications company. Searching qualifications of Dr Johnson include training and experience received during the Doctor of Pharmacy program at the University of Michigan, an American Society of Health-System Pharmacists-accredited pharmacy practice residency completed at the University of Florida, and 3 years performing medical writing and editing as an Associate Editor or Editor with Scientific Therapeutics Information, Inc.

Online literature searches were conducted in MEDLINE (1966-1998), EMBASE (1980-1998), and BIOSIS (1997-1998), with MEDLINE being the primary reference source. All searches were limited to English language. MEDLINE search strategy included the following terms: COX-2 inhibitors, cyclooxygenase-2 inhibitors, cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib, SC-58635, flosulide, nimesulide, SC-58125, L-748731, L-745337, SC-57666, T-614, cyclooxygenase-2 and renal, cyclooxygenase-2 and lung, cyclooxygenase-2 and inflammation, cyclooxygenase-2, COX-2, and cyclooxygenase 2 with wound healing, immune system, or hormone. EMBASE search strategy included the following terms: COX-2 inhibitor, cyclooxygenase-2 inhibitor, cyclo-oxygenase-2 inhibitor, cyclooxygenase-2 and renal, cyclooxygenase-2 and inflammation, cyclooxygenase-2, COX-2. BIOSIS search strategy included the following terms: cyclooxygenase-2, COX-2, cyclooxygenase 2.

Additional reference sources were used when available, including references cited in publications related to this topic. Recent issues of *Gastroenterology*, *Journal of Rheumatology*, *Arthritis and Rheumatism*, and *American Journal of Gastroenterology* were reviewed for abstracts presented at the following annual meetings: Digestive Disease Week (1998), Panamerican Congress of Rheumatology

(1998), American College of Rheumatology (1997), and American College of Gastroenterology (1998), respectively.

Only selected references were used in the development of this document. Although many references were reviewed, only those cited herein are listed in the reference list at the end of the document. All cited references are available from SB upon request.

REFERENCES

REFERENCES

Anderson GD, Hauser SD, McGarity KL, Bremer ME, Isakson PC, Gregory SA. Selective inhibition of cyclooxygenase-2 reverses inflammation and expression of COX-2 and IL-6 in rat adjuvant arthritis. *J Clin Invest.* 1996;97:2672-2679.

Anderson RJ. Rheumatoid arthritis: Clinical features and laboratory. In: Schumacher HR, Klippel JH, Koopman WJ, eds. *Primer on the Rheumatic Diseases.* 10th ed. Atlanta, GA: The Arthritis Foundation; 1993:Chapter 10, Part B.

Asselin E, Drolet P, Fortier MA. Cellular mechanisms involved during oxytocin-induced prostaglandin $F_{2\alpha}$ production in endometrial epithelial cells in vitro: role of cyclooxygenase-2. *Endocrinology.* 1997;138:4798-4805.

Bamba H, Ota S, Kato A, Matsuzaki F. Nonsteroidal anti-inflammatory drugs may delay the repair of gastric mucosa by suppressing prostaglandin-mediated increase of hepatocyte growth factor production. *Biochem Biophys Res Commun.* 1998;245:567-571.

Bany BM, Kennedy TG. Regulation of cyclooxygenase gene expression in rat endometrial stromal cells: the role of epidermal growth factor. *Dev Genet.* 1997;21:109-115.

Beharry K, Modanlou HD, Wold S, Rumney P, Asrat T. Cyclooxygenase (COX)-1 and COX-2 but not nitric oxide synthase (NOS) are upregulated in umbilical cord (UC) vessels in preeclamptic pregnancies (abstract). *Pediatr Res.* 1998;43:45A.

Beiche F, Scheuerer S, Brune K, Geisslinger G, Goppelt-Struebe M. Upregulation of cyclooxygenase-2 mRNA in the rat spinal cord following peripheral inflammation. *FEBS Lett.* 1996;390:165-169.

Belvisi MG, Saunders MA, Haddad EB, et al. Induction of cyclooxygenase-2 by cytokines in human cultured airway smooth muscle cells: novel inflammatory role of this cell type. *Br J Pharmacol.* 1997;120:910-916.

Bjarnason I, Sigthorsson G, Crane R, et al. COX-2 specific inhibition with MK-0966 25 or 50 mg QD does not increase intestinal permeability: a controlled study with placebo (PBO) and indomethacin 50 mg TID (INDO) (abstract). *Am J Gastroenterol.* 1998;93:1670.

Blume ED, Taylor CT, Lennon PF, Stahl GL, Colgan SP. Activated endothelial cells elicit paracrine induction of epithelial chloride secretion: 6-keto-$PGF_{1\alpha}$ is an epithelial secretagogue. *J Clin Invest.* 1998;102:1161-1172.

Boerboom D, Sirois J. Molecular characterization of equine prostaglandin G/H synthase-2 and regulation of its messenger ribonucleic acid in preovulatory follicles. *Endocrinology.* 1998;139:1662-1670.

Brannon TS, MacRitchie AN, Jaramillo MA, et al. Ontogeny of cyclooxygenase-1 and cyclooxygenase-2 gene expression in ovine lung. *Am J Physiol.* 1998;274:L66-L71.

Breder CD. Cyclooxygenase systems in the mammalian brain. *Ann NY Acad Sci.* 1997;813:296-301.

Breder CD, Saper CB. Expression of inducible cyclooxygenase mRNA in the mouse brain after systemic administration of bacterial lipopolysaccharide. *Brain Res.* 1996;713:64-69.

Breder CD, Dewitt D, Kraig RP. Characterization of inducible cyclooxygenase in rat brain. *J Comp Neurol.* 1995;355:296-315.

Brooks DP, Adams J, DePalma PD, Webb EF, Griswold DE, Palmer R. The selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, but not 6MNA, affects renal hemodynamic and renal function in the dog (abstract). *J Invest Med.* 1998;46:227A.

Brunel P, Hornych A, Guyene TT, Sioufi A, Turri M, Ménard J. Renal and endocrine effects of flosulide, after single and repeated administration to healthy volunteers. *Eur J Clin Pharmacol.* 1995;49:193-201.

Brzozowski T, Konturek PC, Pajdo R, Nagraba N, Szczeklik A, Konturek SJ. Role of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) derived prostaglandins (PG) in adaptive cytoprotection induced by mild stress (abstract). *Gastroenterology.* 1998;114:A82.

Caggiano AO, Breder CD, Kraig RP. Long-term elevation of cyclooxygenase-2, but not lipoxygenase, in regions synaptically distant from spreading depression. *J Comp Neurol.* 1996;376:447-462.

Cao C, Matsumura K, Yamagata K, Watanabe Y. Cyclooxygenase-2 is induced in brain blood vessels during fever evoked by peripheral or central administration of tumor necrosis factor. *Brain Res Mol Brain Res.* 1998;56:45-56.

Cao C, Matsumura K, Yamagata K, Watanabe Y. Endothelial cells of the rat brain vasculature express cyclooxygenase-2 mRNA in response to systemic interleukin-1β: a possible site of prostaglandin synthesis responsible for fever. *Brain Res.* 1996;733:263-272.

Cao C, Matsumura K, Yamagata K, Watanabe Y. Induction by lipopolysaccharide of cyclooxygenase-2 mRNA in rat brain: its possible role in the febrile response. *Brain Res.* 1995;697:187-196.

Chan TA, Morin PJ, Vogelstein B, Kinzler KW. Mechanisms underlying nonsteroidal anti-inflammatory drug-mediated apoptosis. *Proc Natl Acad Sci USA.* 1998;95:681-686.

Charette L, Misquitta C, Guay J, Riendeau D, Jones TR. Involvement of cyclooxygenase 2 (COX-2) in intrinsic tone of isolated guinea pig trachea. *Can J Physiol Pharmacol.* 1995;73:1561-1567.

Charpigny G, Reinaud P, Tamby JP, Créminon C, Guillomot M. Cyclooxygenase-2 unlike cyclooxygenase-1 is highly expressed in ovine embryos during the implantation period. *Biol Reprod.* 1997;57:1032-1040.

Chavez R, Bravo C, Zazueta C, et al. Ionophoretic-like properties of ketorolac for calcium. *J Pharmacol Exp Ther.* 1993;267:1134-1139.

Cohn SM, Schloemann S, Tessner T, Seibert K, Stenson WF. Crypt stem cell survival in the mouse intestinal epithelium is regulated by prostaglandins synthesized through cyclooxygenase-1. *J Clin Invest.* 1997;99:1367-1379.

Collaço-Moraes Y, Aspey B, Harrison M, de Belleroche JS. Cyclooxygenase-2 messenger RNA induction in focal cerebral ischemia. *J Cereb Blood Flow Metab.* 1996;16:1366-1372.

Connolly C, McCormick PA, Docherty JR. Effects of the selective cyclooxygenase-2 inhibitor nimesulide on vascular contractions in endothelium-denuded rat aorta. *Eur J Pharmacol.* 1998;352:53-58.

Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. *J Rheumatol.* 1997;24(suppl 49):15-19.

Crofford LJ, Wilder RL, Ristimäki AP, et al. Cyclooxygenase-1 and -2 expression in rheumatoid synovial tissues: effects of interleukin-1β, phorbol ester, and corticosteroids. *J Clin Invest.* 1994;93:1095-1101.

Davies NM. Toxicity of nonsteroidal anti-inflammatory drugs in the large intestine. *Dis Colon Rectum.* 1995;38:1311-1321.

Demoly P, Crampette L, Lebel B, Campbell AM, Mondain M, Bousquet J. Expression of cyclooxygenases 1 and 2 proteins in upper respiratory mucosa. *Clin Exp Allergy.* 1998;28:278-283.

Demoly P, Jaffuel D, Lequeux N, et al. Prostaglandin H synthase 1 and 2 immunoreactivities in the bronchial mucosa of asthmatics. *Am J Respir Crit Care Med.* 1997;155:670-675.

DeWitt DL, Meade E, Smith WL. PGH synthase isoenzyme selectivity: the potential for safer nonsteroidal anti-inflammatory drugs. *Am J Med.* 1993;95(suppl 2A):40S-44S.

Dinchuk JE, Car BD, Focht RJ, et al. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. *Nature.* 1995;378:406-409.

Dirig DM, Konin GP, Isakson PC, Yaksh TL. Effect of spinal cyclooxygenase inhibitors in rat using the formalin test and in vitro prostaglandin E_2 release. *Eur J Pharmacol.* 1997;331:155-160.

Donnelly MT, Hawkey CJ. Review article: COX-II inhibitors – a new generation of safer NSAIDs? *Aliment Pharmacol Ther.* 1997;11:227-236.

Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia. *N Engl J Med.* 1984;310:347-352.

Eckmann L, Stenson WF, Savidge TC, et al. Role of intestinal epithelial cells in the host secretory response to infection by invasive bacteria: bacterial entry induces epithelial prostaglandin H synthase-2 expression and prostaglandin E_2 and $F_{2\alpha}$ production. *J Clin Invest.* 1997;100:296-309.

Ehrlich K, Gretzer B, Respondek M, Peskar BM. Selective inhibition of cyclooxygenase 2 counteracts the protective effect of peptone in the rat stomach (abstract). *Gastroenterology.* 1997;112:A111.

Eis MJ, Watkins BM, Philip A, Welling RE. Nonsteroidal-induced benign strictures of the colon: a case report and review of the literature. *Am J Gastroenterol.* 1998;93:120-121.

Ermert L, Ermert M, Goppelt-Struebe M, et al. Cyclooxygenase isoenzyme localization and mRNA expression in rat lungs. *Am J Respir Cell Mol Biol.* 1998;18:479-488.

Evans JM, McMahon AD, Murray FE, McDevitt DG, MacDonald TM. Nonsteroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut.* 1997;40:619-622.

Fernández-Morata JC, Mullol J, Juan M, et al. Gene expression of COX-1 and COX-2 in human nasal mucosa: modulation by cytokines and steroids (abstract). *Eur Respir J.* 1997;10(suppl):444S.

Ferraz JG, Sharkey KA, Reuter BK, et al. Induction of cyclooxygenase 1 and 2 in the rat stomach during endotoxemia: role in resistance to damage. *Gastroenterology.* 1997;113:195-204.

Fuchs AR, Rust W, Fields MJ. Cyclooxygenase-1 and -2 transcript accumulation in bovine uterine tissues during the second half of pregnancy and parturition (abstract). *Biol Reprod.* 1998;58(suppl 1):122.

Fuentes A, Spaziani EP, O'Brien WF. The expression of cyclooxygenase-2 (COX-2) in amnion and decidua following spontaneous labor. *Prostaglandins.* 1996;52:261-267.

Gibb W, Sun M. Localization of prostaglandin H synthase type 2 protein and mRNA in term human fetal membranes and decidua. *J Endocrinol.* 1996;150:497-503.

Gibson GR, Whitacre EB, Ricotti CA. Colitis induced by nonsteroidal anti-inflammatory drugs: report of four cases and review of the literature. *Arch Intern Med.* 1992;152:625-632.

Gilroy DW, Tomlinson A, Willoughby DA. Differential effects of inhibition of isoforms of cyclooxygenase (COX-1, COX-2) in chronic inflammation. *Inflamm Res.* 1998;47:79-85.

Gretzer B, Ehrlich K, Maricic N, Lambrecht N, Respondek M, Peskar BM. Selective cyclooxygenase-2 inhibitors and their influence on the protective effect of a mild irritant in the rat stomach. *Br J Pharmacol.* 1998a;123:927-935.

Gretzer B, Knorth H, Chantrain M, et al. Effects of diclofenac and L-745,337, a selective cyclooxygenase-2 inhibitor, on prostaglandin E_2 formation in tissue from human colonic mucosa and chronic bursitis (abstract). *Gastroenterology.* 1998b;114:A139.

Guan Y, Chang M, Cho W, et al. Cloning, expression, and regulation of rabbit cyclooxygenase-2 in renal medullary interstitial cells. *Am J Physiol.* 1997;273:F18-F26.

Harding P, Sigmon DH, Alfie ME, et al. Cyclooxygenase-2 mediates increased renal renin content induced by low-sodium diet. *Hypertension.* 1997;29(part 2):297-302.

Harris RC, McKanna JA, Akai Y, Jacobson HR, Dubois RN, Breyer MD. Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases with salt restriction. *J Clin Invest.* 1994;94:2504-2510.

Hartner A, Goppelt-Struebe M, Hilgers KF. Coordinate expression of cyclooxygenase-2 and renin in the rat kidney in renovascular hypertension. *Hypertension.* 1998;31(part 2):201-205.

Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. *N Engl J Med.* 1998;338:727-734.

Hay CH, Trevethick MA, Wheeldon A, Bowers JS, de Belleroche JS. The potential role of spinal cord cyclooxygenase-2 in the development of Freund's complete adjuvant-induced changes in hyperalgesia and allodynia. *Neuroscience.* 1997;78:843-850.

Hayaishi O. Molecular mechanism of sleep-wake regulation: roles of prostaglandins D_2 and E_2. *FASEB J.* 1991;5:2575-2581.

Heerdink ER, Leufkens HG, Herings RMC, Ottervanger JP, Stricker BHC, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Intern Med.* 1998;158:1108-1112.

Hendel J, Nielsen OH. Expression of cyclooxygenase-2 mRNA in active inflammatory bowel disease. *Am J Gastroenterol.* 1997;92:1170-1173.

Holmes DR, Wester W, Thompson RW, Reilly JM. Prostaglandin E_2 synthesis and cyclooxygenase expression in abdominal aortic aneurysms. *J Vasc Surg.* 1997;25:810-815.

Holtz ML, Kindy MS, Craddock S, Moore RW, Pettigrew LC. Induction of PGH synthase and c-*fos* mRNA during early reperfusion of ischemic rat brain. *Mol Brain Res.* 1996;35:339-343.

Houston MC, Weir M, Gray J, et al. The effects of nonsteroidal anti-inflammatory drugs on blood pressures of patients with hypertension controlled by verapamil. *Arch Intern Med.* 1995;155:1049-1054.

Hunt R, Bowen B, James C, et al. COX-2 specific inhibition with MK-0966 25 or 50 mg QD over 4 weeks does not increase fecal blood loss: a controlled study with placebo and ibuprofen 800 mg TID (abstract). *Am J Gastroenterol.* 1998;93:1671.

Iadecola C, Ross ME. Role of iNOS and COX-2 gene expression in ischemic brain injury (abstract). *J Neurochem.* 1998;70(suppl 1):S17.

Ichitani Y, Shi T, Haeggstrom JZ, Samuelsson B, Hökfelt T. Increased levels of cyclooxygenase-2 mRNA in the rat spinal cord after peripheral inflammation: an in situ hybridization study. *Neuroreport.* 1997;8:2949-2952.

Iñiguez MA, Pablos JL, Carreira PE, Cabré F, Gomez-Reino JJ. Detection of COX-1 and COX-2 isoforms in synovial fluid cells from inflammatory joint diseases. *Br J Rheumatol.* 1998;37:773-778.

Insel PA. Analgesic-antipyretics and anti-inflammatory agents: drugs employed in the treatment of rheumatoid arthritis and gout. In: Goodman Gilman A, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 8th ed. Elmsford, NY: Pergamon Press, Inc; 1990:638-681.

Johnson AG, Simons LA, Simons J, Friedlander Y, McCallum J. Nonsteroidal anti-inflammatory drugs and hypertension in the elderly: a community-based cross-sectional study. *Br J Clin Pharmacol.* 1993;35:455-459.

Jouzeau JY, Terlain B, Abid A, Nédélec E, Netter P. Cyclooxygenase isoenzymes: how recent findings affect thinking about nonsteroidal anti-inflammatory drugs. *Drugs.* 1997;53:563-582.

Kaplan B, Swain RA. NSAIDs: are there any differences? *Arch Fam Med.* 1993;2:1167-1174.

Kargman S, Charleson S, Cartwright M, et al. Characterization of prostaglandin G/H synthase 1 and 2 in rat, dog, monkey, and human gastrointestinal tracts. *Gastroenterology.* 1996;111:445-454.

Kato T, Ishiguro N, Iwata H, Kojima T, Ito T, Naruse K. Upregulation of COX-2 expression by uni-axial cyclic stretch in human lung fibroblast cells. *Biochem Biophys Res Commun.* 1998;244:615-619.

Kaufman HL, Fischer AH, Carroll M, Becker JM. Colonic ulceration associated with nonsteroidal anti-inflammatory drugs: report of three cases. *Dis Colon Rectum.* 1996;39:705-710.

Kaufmann WE, Andreasson KI, Isakson PC, Worley PF. Cyclooxygenases and the central nervous system. *Prostaglandins.* 1997;54:601-624.

Kaufmann WE, Worley PF, Pegg J, Bremer M, Isakson P. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. *Proc Natl Acad Sci USA.* 1996;93:2317-2321.

Kishimoto Y, Wada K, Nakamoto K, Kawasaki H, Hasegawa J. Levels of cyclooxygenase-1 and –2 mRNA expression at various stages of acute gastric injury induced by ischemia-reperfusion in rats. *Arch Biochem Biophys.* 1998;352:153-157.

Kishimoto Y, Wada K, Nakamoto K, et al. Quantitative analysis of cyclooxygenase-2 gene expression on acute gastric injury induced by ischemia-reperfusion in rats. *Life Sci.* 1997;60:127-133.

Klein T, Ullrich V, Pfeilschifter J, Nüsing R. On the induction of cyclooxygenase-2, inducible nitric oxide synthase and soluble phospholipase A_2 in rat mesangial cells by a nonsteroidal anti-inflammatory drug: the role of cyclic AMP. *Mol Pharmacol.* 1998;53:385-391.

Kömhoff M, Gröne H-J, Klein T, Seyberth HW, Nüsing RM. Localization of cyclooxygenase-1 and -2 in adult and fetal human kidney: implication for renal function. *Am J Physiol.* 1997;272:F460-F468.

Kowalski ML, Kowalewski R, Pawliczak R, Woszczek J, Grzegorczyk J. Human nasal epithelial cells cultured from nasal polyps express both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) mRNA (abstract). *Eur Respir J.* 1997;10(suppl):255S.

Lancaster-Smith MJ, Jaderberg ME, Jackson DA. Ranitidine in the treatment of nonsteroidal anti-inflammatory drug associated gastric and duodenal ulcers. *Gut.* 1991;32:252-255.

Langenbach R, Morham SG, Tiano HF, et al. Prostaglandin synthase 1 gene disruption in mice reduces arachidonic acid-induced inflammation and indomethacin-induced gastric ulceration. *Cell.* 1995;83:483-492.

Lanza F, Simon T, Quan H, et al. Selective inhibition of cyclooxygenase-2 (COX-2) with MK-0966 (250 mg QD) is associated with less gastroduodenal damage than aspirin (ASA) 650 mg QID or ibuprofen (IBU) 800 mg TID (abstract). *Gastroenterology.* 1997a;112:A194.

Lanza FL, Rack MF, Callison DA, et al. A pilot endoscopic study of the gastroduodenal effects of SC-58635, a novel COX-2-selective inhibitor (abstract). *Gastroenterology.* 1997b;112:A194.

Li DY, Hardy P, Abran D, et al. Key role for cyclooxygenase-2 in PGE_2 and $PGF_{2\alpha}$ receptor regulation and cerebral blood flow of the newborn. *Am J Physiol.* 1997;273:R1283-R1290.

Lichtenberger LM, Wang ZM, Romero JJ, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) associate with zwitterionic phospholipids: insight into the mechanism and reversal of NSAID-induced gastrointestinal injury. *Nat Med.* 1995;1:602-603.

Lim H, Paria BC, Das SK, et al. Multiple female reproductive failures in cyclooxygenase 2-deficient mice. *Cell.* 1997;91:197-208.

Liu J, Carrière PD, Doré M, Sirois J. Prostaglandin G/H synthase-2 is expressed in bovine preovulatory follicles after the endogenous surge of luteinizing hormone. *Biol Reprod.* 1997;57:1524-1531.

Lugea A, Antolin M, Mourelle M, Guarner F, Malagelada JR. Deranged hydrophobic barrier of the rat gastroduodenal mucosa after parenteral nonsteroidal anti-inflammatory drugs. *Gastroenterology.* 1997;112:1931-1939.

Macchia L, Di Paola R, Guerrese MC, et al. Expression of prostaglandin endoperoxide H synthase 1 and 2 in human placenta at term. *Biochem Biophys Res Commun.* 1997;233:496-501.

Mahida YR, Beltinger J, Makh S, et al. Adult human colonic subepithelial myofibroblasts express extracellular matrix proteins and cyclooxygenase-1 and -2. *Am J Physiol.* 1997;273:G1341-G1348.

Mahmud T, Scott DL, Bjarnason I. A unifying hypothesis for the mechanism of NSAID related gastrointestinal toxicity. *Ann Rheum Dis.* 1996;55:211-213.

Majerus PW. Prostaglandins: critical roles in pregnancy and colon cancer. *Curr Biol.* 1998;8:R87-R89.

Majima M, Isono M, Ikeda Y, et al. Significant roles of inducible cyclooxygenase (COX)-2 in angiogenesis in rat sponge implants. *Jpn J Pharmacol.* 1997;75:105-114.

Marcheselli VL, Bazan NG. Sustained induction of prostaglandin endoperoxide synthase-2 by seizures in hippocampus. *J Biol Chem.* 1996;271:24794-24799.

Maricic N, Ehrlich K, Schuligoi R, Respondek M, Peskar BM. Cyclooxygenase-2-derived prostaglandins contribute to mucosal resistance to ischemia/reperfusion injury in the rat stomach (abstract). *Gastroenterology*. 1998;114:A215.

Marini U, Spotti D. Gastric tolerability of nimesulide: a double-blind comparison of 2 oral dosage regimens and placebo. *Drugs*. 1993;46(suppl 1):249-252.

Matsumura K, Cao C, Watanabe Y. Possible role of cyclooxygenase-2 in the brain vasculature in febrile response. *Ann NY Acad Sci*. 1997;813:302-306.

McCown TJ, Knapp DJ, Crews FT. Inferior collicular seizure generalization produces site-selective cortical induction of cyclooxygenase-2 (COX-2). *Brain Res*. 1997;767:370-374.

McKanna JA, Zhange MZ, Wang JL, Cheng HF, Harris RC. Constitutive expression of cyclooxygenase-2 in rat vas deferens. *Am J Physiol*. 1998;275:R227-R233.

Mizuno H, Sakamoto C, Matsuda K, et al. Induction of cyclooxygenase 2 in gastric mucosal lesions and its inhibition by the specific antagonist delays healing in mice. *Gastroenterology*. 1997;112:387-397.

Morham SG, Langenbach R, Loftin CD, et al. Prostaglandin synthase 2 gene disruption causes severe renal pathology in the mouse. *Cell*. 1995;83:473-482.

Morteau O, Morham S, Sellon R, Smithies O, Sartor RB. Absence of spontaneous gastrointestinal inflammation in cyclooxygenase-1 and in cyclooxygenase-2 deficient mice (abstract). *Gastroenterology*. 1997a;112:A1045.

Morteau O, Morham S, Sellon R, Boroviov J, Smithies O, Sartor RB. Genetic deficiency in cyclooxygenase-2 but not in cyclooxygenase-1 exacerbates DSS-induced acute colitis in mice (abstract). *Gastroenterology*. 1997b;112:A1046.

Nogawa S, Zhang F, Ross ME, Iadecola C. Cyclooxygenase-2 gene expression in neurons contributes to ischemic brain damage. *J Neurosci*. 1997;17:2746-2755.

Norwood VF. Progressive postnatal renal dysplasia in cyclooxygenase-2 deficient mice (abstract 1828). *Pediatr Res*. 1998;43(4 Part 2):312A.

O'Neill GP, Ford-Hutchinson AW. Expression of mRNA for cyclooxygenase-1 and cyclooxygenase-2 in human tissues. *FEBS Lett.* 1993;330:156-160.

Onoe Y, Miyaura C, Kaminakayashiki T, et al. IL-13 and IL-4 inhibit bone resorption by suppressing cyclooxygenase-2-dependent prostaglandin synthesis in osteoblasts. *J Immunol.* 1996;156:758-764.

Öst M, Uhl E, Carlsson M, Gidlöf A, Söderkvist P, Sirsjö A. Expression of mRNA for phospholipase A_2, cyclooxygenases, and lipoxygenases in cultured human umbilical vascular endothelial and smooth muscle cells and in biopsies from umbilical arteries and veins. *J Vasc Res.* 1998;35:150-155.

Osuka K, Suzuki Y, Watanabe Y, Takayasu M, Yoshida J. Inducible cyclooxygenase expression in canine basilar artery after experimental subarachnoid hemorrhage. *Stroke.* 1998;29:1219-1222.

Pang L, Knox AJ. Effect of interleukin-1β, tumour necrosis factor-α and interferon-γ on the induction of cyclooxygenase-2 in cultured human airway smooth muscle cells. *Br J Pharmacol.* 1997a;121:579-587.

Pang L, Knox AJ. PGE_2 release by bradykinin in human airway smooth muscle cells: involvement of cyclooxygenase-2 induction. *Am J Physiol.* 1997b;273:L1132-L1140.

Parfenova H, Eidson TH, Leffler CW. Upregulation of COX-2 in cerebral microvascular endothelial cells by smooth muscle cell signals. *Am J Physiol.* 1997;273:C277-C288.

Park JM, Yang T, Arend LJ, Smart AM, Schnermann JB, Briggs JP. Cyclooxygenase-2 is expressed in bladder during fetal development and stimulated by outlet obstruction. *Am J Physiol.* 1997;273:F538-F544.

Peri KG, Hardy P, Li DY, Varma DR, Chemtob S. Prostaglandin G/H synthase-2 is a major contributor of brain prostaglandins in the newborn. *J Biol Chem.* 1995;270:24615-24620.

Piazza GA, Alberts DS, Hixson LJ, et al. Sulindac sulfone inhibits azoxymethane-induced-colon carcinogenesis in rats without reducing prostaglandin levels. *Cancer Res.* 1997;57:2909-2915.

Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med.* 1993;153:477-484.

Resnick DK, Graham SH, Dixon CE, Marion DW. The role of cyclooxygenase 2 in acute spinal cord injury (abstract). *J Neurotrauma.* 1998;15:20.

Reuter BK, Asfaha S, Buret A, Sharkey KA, Wallace JL. Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2. *J Clin Invest.* 1996;98:2076-2085.

Richards JS. Editorial: sounding the alarm – does induction of prostaglandin endoperoxide synthase-2 control the mammalian ovulatory clock? *Endocrinology.* 1997;138:4047-4048.

Rimarachin JA, Jacobson JA, Szabo P, Maclouf J, Creminon C, Weksler BB. Regulation of cyclooxygenase-2 expression in aortic smooth muscle cells. *Arterioscler Thromb.* 1994;14:1021-1031.

Rossat J, Maillard M, Nussberger J, Drower E, Brunner H-R, Burnier M. Acute renal effects of selective inhibition of cyclooxygenase-2 in healthy salt-depleted subjects (abstract). *J Am Soc Nephrol.* 1998;9:346A.

Sairanen T, Ristimäki A, Karjalainen-Lindsberg ML, Paetau A, Kaste M, Lindsberg PJ. Cyclooxygenase-2 is induced globally in infarcted human brain. *Ann Neurol.* 1998;43:738-747.

San Miguel P, Laudanno OM, Guastalli G, Esnarriaga JM, Cesolari JA. Anti-inflammatory drugs: COX-2 selective and stress-induced gastric lesions (abstract). *Gastroenterology.* 1998;114:A276.

Sano H, Hla T, Maier JA, et al. In vivo cyclooxygenase expression in synovial tissues of patients with rheumatoid arthritis and osteoarthritis and rats with adjuvant and streptococcal cell wall arthritis. *J Clin Invest.* 1992;89:97-108.

Sarrazin P, de Brum-Fernandes AJ. Isolation of mature human osteoclasts and characterization of cyclooxygenase isoforms expression (abstract). *Bone.* 1998;23(suppl):S338.

Sasaki E, Pai R, Komurasaki T, et al. Induction of cyclooxygenase-2 in rat gastric epithelial cells by EGF, epiregulin and bFGF (abstract). *Gastroenterology*. 1998;114:A277.

Sato T, Kirimura Y, Mori Y. The co-culture of dermal fibroblasts with human epidermal keratinocytes induces increased prostaglandin E_2 production and cyclooxygenase-2 activity in fibroblasts. *J Invest Dermatol*. 1997;109:334-339.

Sawaoka H, Tsuji S, Tsujii M, et al. Expression of the cyclooxygenase-2 gene in gastric epithelium. *J Clin Gastroenterol*. 1997;25(suppl 1):S105-S110.

Schmassmann A. Mechanisms of ulcer healing and effects of nonsteroidal anti-inflammatory drugs. *Am J Med*. 1998;104(suppl 3A):43S-51S.

Schmassmann A, Peskar BM, Stettler C, et al. Effects of inhibition of prostaglandin endoperoxide synthase-2 in chronic gastrointestinal ulcer models in rats. *Br J Pharmacol*. 1998;123:795-804.

Schmassmann A, Tarnawski A, Peskar BM, Varga L, Flogerzi B, Halter H. Influence of acid and angiogenesis on kinetics of gastric ulcer healing in rats: interaction with indomethacin. *Am J Physiol*. 1995;268:G276-G285.

Schneider A, Stahl RAK. Cyclooxygenase-2 (COX-2) and the kidney: current status and potential perspectives. *Nephrol Dial Transplant*. 1998;13:10-12.

Seibert K, Zhang Y, Leahy K, et al. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. *Proc Natl Acad Sci USA*. 1994;91:12013-12017.

Shah AA, Murray FE, Thjodleifsson B, et al. Nimesulide, a selective COX-2 inhibitor, causes less gastrointestinal damage compared with naproxen: a prospective study in human volunteers (abstract). *Gastroenterology*. 1998;114:A283.

Shigeta J, Takahashi S, Ishikawa M, Okabe S. Role of cyclooygenase-2 (COX-2) in the healing of gastric ulcers in rats (abstract). *Gastroenterology*. 1998;114:A285.

Singer II, Kawka DW, Schloemann S, Tessner T, Riehl T, Stenson WF. Cyclooxygenase 2 is induced in colonic epithelial cells in inflammatory bowel disease. *Gastroenterology*. 1998;115:297-306.

Sirois J. Induction of prostaglandin endoperoxide synthase-2 by human chorionic gonadotropin in bovine preovulatory follicles in vivo. *Endocrinology*. 1994;135:841-848.

Sirois J, Doré M. The late induction of prostaglandin G/H synthase-2 in equine preovulatory follicles supports its role as a determinant of the ovulatory process. *Endocrinology*. 1997;138:4427-4434.

Sirois J, Richards JS. Purification and characterization of a novel, distinct isoform of prostaglandin endoperoxide synthase induced by human chorionic gonadotropin in granulosa cells of rat preovulatory follicles. *J Biol Chem*. 1992;267:6382-6388.

Slater DM, Allport V, Bennett P. Changes in the expression of the type-2 but not the type-1 cyclooxygenase enzyme in chorion-decidua with the onset of labour. *Br J Obstet Gynaecol*. 1998;105:745-748.

Slater DM, Berger LC, Newton R, Moore GE, Bennett PR. Expression of cyclooxygenase types 1 and 2 in human fetal membranes at term. *Am J Obstet Gynecol*. 1995;172:77-82.

Slater DM, Berger LC, Moore GE, Bennett PR. Implication of mRNA binding proteins in the regulation of cyclooxygenase in human amnion at term. *Biochem Biophys Res Commun*. 1994;203:67-71.

Smith G, Roberts R, Hall C, Nuki G. Reversible ovulatory failure associated with the development of luteinized unruptured follicles in women with inflammatory arthritis taking nonsteroidal anti-inflammatory drugs. *Br J Rheumatol*. 1996;35:458-462.

Smith WL, DeWitt DL. Biochemistry of prostaglandin endoperoxide H synthase-1 and synthase-2 and their differential susceptibility to nonsteroidal anti-inflammatory drugs. *Semin Nephrol*. 1995;15:179-194.

Somasundaram S, Rafi S, Hayllar J, et al. Mitochondrial damage: a possible mechanism of the "topical" phase of NSAID-induced injury to rat intestine. *Gut*. 1997;41:344-353.

Song JH, Sirois J, Houde A, Murphy BD. Cloning, developmental expression, and immunohistochemistry of cyclooxygenase 2 in the endometrium during embryo implantation and gestation in the mink (*Mustela vison*). *Endocrinology*. 1998;139:3629-3636.

Sorli CH, Zhang HJ, Armstrong MB, Rajotte RV, Maclouf J, Robertson RP. Basal expression of cyclooxygenase-2 and nuclear factor-interleukin 6 are dominant and coordinately regulated by interleukin 1 in the pancreatic islet. *Proc Natl Acad Sci USA*. 1998;95:1788-1793.

Stamm C, Burkhalter E, Pearce W, et al. Benign colonic ulcers associated with nonsteroidal anti-inflammatory drug ingestion. *Am J Gastroenterol*. 1994;89:2230-2233.

Steinhäuslin F, Munafo A, Buclin T, Macciocchi A, Biollaz J. Renal effects of nimesulide in furosemide-treated subjects. *Drugs*. 1993;46(suppl 1):257-262.

Stenson WF. Cyclooxygenase 2 and wound healing in the stomach (editorial). *Gastroenterology*. 1997;112:645-648.

Swaisgood CM, Zu HX, Perkins DJ, et al. Coordinate expression of inducible nitric oxide synthase and cyclooxygenase-2 genes in uterine tissues of endotoxin-treated pregnant mice. *Am J Obstet Gynecol*. 1997;177:1253-1262.

Szczeklik A. Anti-cyclooxygenase agents and asthma. *J Asthma*. 1983;20:23-29.

Tarnawski A, Kidao J, Jaafar S, et al. Expression and localization of cyclooxygenase-2 in normal and ulcerated human gastric mucosa, and in cultured human endothelial cells (abstract). *Gastroenterology*. 1997;112:A309.

Tocco G, Freire-Moar J, Schreiber SS, Sakhi SH, Aisen PS, Pasinetti GM. Maturational regulation and regional induction of cyclooxygenase-2 in rat brain: implications for Alzheimer's disease. *Exp Neurol*. 1997;144:339-349.

Townend JN, Doran J, Lote CJ, Davies MK. Peripheral haemodynamic effects of inhibition of prostaglandin synthesis in congestive heart failure and interactions with captopril. *Br Heart J*. 1995;73:434-441.

Tsuji M, DuBois RN. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. *Cell*. 1995;83:493-501.

Tsuji S, Sun WH, Sawaoka H, et al. A specific inhibitor for cyclooxygenase-2 delays gastric ulcer healing (abstract). *Gastroenterology*. 1997;112:A316.

Twomey BM, Dale MM. Cyclooxygenase-independent effects of nonsteroidal anti-inflammatory drugs on the neutrophil respiratory burst. *Biochem Pharmacol*. 1992;43:413-418.

Ukawa H, Hirata T, Kobayashi H, Yamakuni H, Takeuchi K. Effects of COX-2-selective and NO-releasing NSAIDs on mucosal ulcerogenic and healing responses in rat stomachs (abstract). *Gastroenterology*. 1997;112:A317.

Vadas P, Stefanski E, Wloch M, Grouix B, Van Den Bosch H, Kennedy B. Secretory non-pancreatic phospholipase A_2 and cyclooxygenase-2 expression by tracheobronchial smooth muscle cells. *Eur J Biochem*. 1996;235:557-563.

Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol*. 1998;38:97-120.

Viganò T, Habib A, Hernandez A, et al. Cyclooxygenase-2 and synthesis of PGE_2 in human bronchial smooth-muscle cells. *Am J Respir Crit Care Med*. 1997;155:864-868.

Viñals M, Martínez-González J, Badimon JJ, Badimon L. HDL-induced prostacyclin release in smooth muscle cells is dependent on cyclooxygenase-2 (COX-2). *Arterioscler Thromb Vasc Biol*. 1997;17:3481-3488.

Von Knethen A, Brüne B. Cyclooxygenase-2: an essential regulator of NO-mediated apoptosis. *FASEB J*. 1997;11:887-895.

Walan A, Bader J-P, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N Engl J Med*. 1989;320:69-75.

Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology*. 1997;112:1000-1016.

Wallace JL, Bak A, McKnight W, Asfaha S, Sharkey KA, MacNaughton WK. Cyclooxygenase 1 contributes to inflammatory responses in rats and mice: implications for gastrointestinal toxicity. *Gastroenterology*. 1998;115:101-109.

Wetzka B, Nüsing R, Charnock-Jones DS, Schäfer W, Zahradnik HP, Smith SK. Cyclooxygenase-1 and -2 in human placenta and placental bed after normal and preeclamptic pregnancies. *Hum Reprod.* 1997;12:2313-2320.

Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol.* 1991;31:588-598.

Wilborn J, Crofford LJ, Burdick MD, Kunkel SL, Strieter RM, Peters-Golden M. Cultured lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis have a diminished capacity to synthesize prostaglandin E_2 and to express cyclooxygenase-2. *J Clin Invest.* 1995;95:1861-1868.

Willingale HL, Gardiner NJ, McLymont N, Giblett S, Grubb BD. Prostanoids synthesized by cyclooxygenase isoforms in rat spinal cord and their contribution to the development of neuronal hyperexcitability. *Br J Pharmacol.* 1997;122:1593-1604.

Wong SCY, Fukuchi M, Melnyk P, Rodger I, Giaid A. Induction of cyclooxygenase-2 and activation of nuclear factor-κB in myocardium of patients with congestive heart failure. *Circulation.* 1998;98:100-103.

Wu KK. Cyclooxygenase-2 induction in congestive heart failure: friend or foe? *Circulation.* 1998;98:95-96.

Xiao CW, Murphy BD, Sirois J, Goff AK. Downregulation of oxytocin receptor and oxytocin-induced prostaglandin secretion, COX-2 and prostaglandin F synthase expression by interferon-τ bovine endometrial cells in vitro (abstract). *Biol Reprod.* 1998;58(suppl 1):174.

Yamagata K, Andreasson KI, Kaufmann WE, Barnes CA, Worley PF. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. *Neuron.* 1993;11:371-386.

Yamamoto T, Nozaki-Taguchi N. Analysis of the effects of cyclooxygenase (COX)-1 and COX-2 in spinal nociceptive transmission using indomethacin, a nonselective COX inhibitor, and NS-398, a COX-2 selective inhibitor. *Brain Res.* 1996;739:104-110.

Yang T, Singh I, Pham H, et al. Regulation of cyclooxygenase expression in the kidney by dietary salt intake. *Am J Physiol.* 1998;274:F481-F489.

Yeomans ND, Cook GA, Giraud AS. Selective COX-2 inhibitors: are they safe for the stomach? (editorial). *Gastroenterology*. 1998;115:227-229.

Zabel-Langhennig A, Holler B, Engeland K, Mössner J. Regulation of transcription of the two cyclooxygenase isoforms in pancreas acini (abstract). *Gastroenterology*. 1998;114:A512.

Zhang M-Z, Wang J-L, Cheng H-F, Harris RC, McKanna JA. Cyclooxygenase-2 in rat nephron development. *Am J Physiol*. 1997;273:F994-F1002.

Zuo J, Lei ZM, Rao CV, Pietrantoni M, Cook VD. Differential cyclooxygenase-1 and -2 gene expression in human myometria from preterm and term deliveries. *J Clin Endocrinol Metab*. 1994;79:894-899.

EXECUTIVE SUMMARY

Celecoxib (tradename Celebrex™) is an oral anti-inflammatory and analgesic product intended for use in the treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) and for the management of pain. It was developed to provide anti-inflammatory and analgesic effects comparable to commonly used non-steroidal anti-inflammatory agents drugs (NSAIDs) but without the gastrointestinal and platelet effects of NSAIDs. The clinical development program for celecoxib included more than 13,000 patients and healthy volunteers enrolled in over 50 different studies. The overall results of this clinical program demonstrated that celecoxib is comparable in efficacy to naproxen and is superior to naproxen, diclofenac and ibuprofen in the occurrence of upper gastrointestinal (UGI) ulceration, ulcer complications and effects on platelets. Further, celecoxib was not found to be associated with increases in other clinically significant adverse reactions compared to NSAIDs. Thus, celecoxib has been shown to provide a significant therapeutic benefit over commonly prescribed NSAIDs used in the treatment of OA, RA and pain.

Celecoxib is a highly selective inhibitor of cyclooxygenase-2 (COX-2), one of two known isoforms of cyclooxygenase: COX-1 and COX-2. Commonly used NSAIDs such as aspirin, naproxen and ibuprofen are non-selective inhibitors of COX-1 and COX-2. (1) They are effective anti-arthritic agents but produce clinically-limiting side effects due to their inhibition of COX-1 at therapeutic doses. (2-4)

The clinical program examined the human pharmacokinetics, efficacy, and safety profile of celecoxib with a focus on its effects on the GI tract, platelets and kidney.

Celecoxib is a low solubility, high permeability drug that is rapidly absorbed, has a large volume of distribution (consistent with high tissue uptake) and is extensively metabolized by the liver to inactive metabolites that are excreted primarily in the feces and to a lesser extent in the urine. Pharmacokinetics are linear; the elimination half life is about 10 hours and steady state levels are reached by five days with the therapeutic dose and regimen. The pharmacokinetics in subgroup populations such as the elderly were studied and well described. No clinically significant drug-drug interactions were observed with compounds commonly used by the intended patient population, including warfarin and methotrexate.

Five pivotal trials of 6 or 12 weeks duration uniformly showed that celecoxib was superior to placebo in treating OA of the knee and/or hip and similar to a full therapeutic dose of naproxen. Maximal efficacy was obtained with 200 mg per day administered as a single dose or divided doses. Replicate 12-week studies showed that celecoxib at 100 mg or 200 mg BID was superior to placebo in treating RA and similar to naproxen. A 6-month trial confirmed the durability of response with celecoxib. The data from four

trials using an acute post-surgery pain model and the chronic pain data from the aforementioned arthritis trials collectively demonstrated that celecoxib has analgesic properties. The post-oral surgery studies showed that celecoxib had an onset of action within one hour and significant relief of OA pain was demonstrated within 24 hours after the first dose.

Over 4,500 patients with OA or RA participated in endoscopy trials designed to compare the incidence of UGI ulceration between celecoxib, NSAIDs and placebo. In two 12-week studies with Baseline and end-of-study endoscopies, the ulcer incidence with celecoxib at full therapeutic doses, as well as at 2-4 times the full therapeutic dose, was not significantly different from placebo but significantly lower than with naproxen. The superior GI safety of celecoxib compared to naproxen was confirmed by a 12-week serial endoscopy trial. Another 12-week serial endoscopy study demonstrated a significantly lower ulcer incidence with celecoxib compared to ibuprofen and a 6-month trial showed a significantly lower incidence of ulcers with celecoxib compared to diclofenac.

The endoscopy results were corroborated by a blinded tabulation of clinically significant UGI events (bleeding, perforation, and gastric outlet obstruction) that occurred during controlled studies. The analysis demonstrated an annual incidence of ulcer complications for celecoxib of 0.20% that was significantly less than the 1.68% seen with NSAIDs, but similar to placebo. The incidence of clinically significant UGI events for celecoxib was confirmed by an analysis of data from a large open-label safety trial.

Celecoxib was also differentiated from NSAIDs in terms of its effects on platelets, that contain only the COX-1 isoform. At doses up to 6-12 times the full therapeutic dose, celecoxib had no significant effect on platelet aggregation or bleeding time. In contrast, NSAIDs consistently and significantly inhibited platelet aggregation and prolonged bleeding time at typical therapeutic doses.

The safety of celecoxib was evaluated based on the experience with all the patients and healthy subjects who participated in clinical trials. Chronic dosing in arthritis patients ranged from 100 mg BID to 400 mg BID for periods in excess of 12 months. A dose as high as 1200 mg BID was used in certain safety/pharmacology studies. Total exposure exceeds 3,000 patient years and 981 patients have completed at least one year of treatment. Overall, celecoxib was well tolerated. GI symptoms (dyspepsia, nausea, abdominal pain) were more common in patients receiving celecoxib than in patients on placebo, but significantly less than in patients on NSAIDs. Renal adverse events were uncommon and occurred no more frequently than in patients on NSAIDs. Clinical laboratory test results indicated that celecoxib did not have adverse hematologic or hepatic effects.

In sum, celecoxib is equivalent to NSAIDs in terms of therapeutic effectiveness (a function of the inhibition of COX-2), but lacks the characteristic COX-1 dependent toxicities of NSAIDs on the GI tract and platelets. In general, celecoxib was safe and well tolerated. These results clearly establish the wide clinical therapeutic index of celecoxib and clinical utility of this new agent in the treatment of OA, RA, and pain.

THIS PAGE INTENTIONALLY LEFT BLANK

TABLE OF CONTENTS

TABLES

FIGURES

GLOSSARY

Abbreviation	Definition
ACR	American College of Rheumatology
APS	American Pain Society
BID	Two Times per Day
BUN	Blood Urea Nitrogen
COX	Cyclooxygenase
DMARD	Disease-Modifying Antirheumatic Drug
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HAQ	Health Assessment Questionnaire
IND	Investigational New Drug Application
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LS Mean	Least Square Mean
MI	Myocardial Infarction
NDA	New Drug Application
NSAID	Non-steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OASI	Osteoarthritis Severity Index
PD	Pharmacodynamic
PG	Prostaglandin
PID	Pain Intensity Difference
PK	Pharmacokinetic
PR	Pain Relief
PRA	Plasma Renin Activity
PRID	Sum of Pain Relief and Pain Intensity Difference
PRN	As Needed
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Once per Day
QID	Four Times per Day
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
SD	Single Dose
TID	Three Times per Day
Tx	Thromboxane
UGI	Upper Gastrointestinal
URTI	Upper Respiratory Tract Infection
VAS	Visual Analog Scale
WBC	White Blood Cell
WOMAC	Western Ontario and McMaster Universities OA Index

1.0 OVERVIEW

Celecoxib (tradename Celebrex™) is a specific cyclooxygenase-2 (COX-2) inhibitor with anti-inflammatory and analgesic activity.

Non-steroidal anti-inflammatory drugs (NSAIDs) possess anti-inflammatory, analgesic, and antipyretic activity, and are widely used to treat osteoarthritis (OA), rheumatoid arthritis (RA), and pain. However, these agents cause upper gastrointestinal (UGI) mucosal damage and side effects related to platelet and renal function that limit use in a significant number of patients. (2-4) NSAIDs are known to inhibit the enzyme cyclooxygenase (COX) resulting in a reduction in prostaglandin (PGs) production. (5,6) Recently, two distinct COX isoforms were identified: 1) a constitutive form (COX-1), present in most tissues including the GI mucosa and platelets, that produces PGs necessary for normal physiological function (6,7) and 2) an inducible form (COX-2) that is primarily expressed in association with inflammation. (8,9) Our hypothesis is that constitutive COX-1 activity protects the GI tract and maintains normal platelet function whereas inducible COX-2 activity is responsible for inflammation and pain. Therefore, specific inhibitors of COX-2 will be anti-inflammatory and analgesic without having the mechanism-based side effects of NSAIDs.

Nonclinical in vitro and in vivo studies have demonstrated that celecoxib is a specific inhibitor of COX-2. (10) In animal studies, celecoxib was shown to have anti-inflammatory and analgesic effects equivalent to NSAIDs, and to inhibit maximally COX-2 derived PG formation while sparing PG production in the GI tract. The compound underwent extensive toxicological evaluations, including acute, subchronic, chronic, genetic, and reproductive toxicology, as well as carcinogenicity testing. No novel toxicity was observed, and the established safety margins suggested that celecoxib had a pharmacological profile that would allow rigorous testing in humans.

Subsequently, the clinical development program was undertaken to:

- determine the pharmacokinetic properties of celecoxib in humans;
- establish the efficacy of celecoxib in treating the signs and symptoms of OA and RA;
- establish the efficacy of celecoxib in the management of pain;

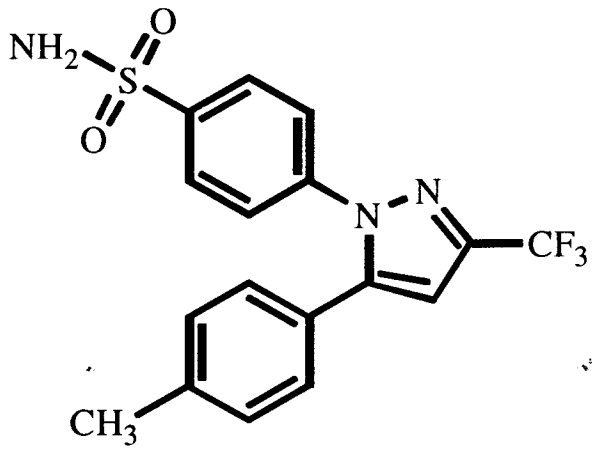
- compare the effects of celecoxib with that of NSAIDs and placebo on the UGI mucosa, platelet function, and renal function; and
- assess the safety and tolerability of celecoxib in patient populations in whom its use is indicated.

2.0 BACKGROUND

2.1 Pharmacological Class

Celecoxib is a novel diarylsubstituted pyrazole that selectively inhibits COX-2. The chemical name of the compound is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide. Celecoxib has a molecular weight of 381.38. The chemical structure is depicted in Figure 1.

Figure 1. Chemical Structure of Celecoxib ($C_{17}H_{14}F_3N_3O_2S$)



Celecoxib selectively inhibits COX-2 through the time-dependent formation of a tight enzyme-inhibitor complex that is noncovalent but slowly dissociable. Celecoxib has a low affinity for the constitutively expressed isoform COX-1. Consequently, at therapeutic doses, celecoxib has no measurable effect on prostanoids synthesized by COX-1 and does not interfere with normal COX-1 regulated processes.

The World Health Organization (WHO) working group on anatomical therapeutic chemical (ATC) classification recently assigned selective inhibitors of COX-2 to a new ATC category for anti-inflammatory agents. The category recognizes the differentiation of COX-2 inhibitors from classic NSAIDs on the basis of their pharmacologic activity.

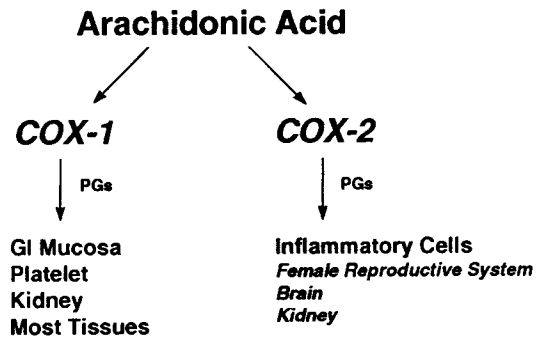
2.2 Scientific Rationale

2.2.1 Mechanism of the Inherent Risks of Current Therapy

Currently, NSAIDs are the most common class of agents used to treat the signs and symptoms of arthritis and pain. The NSAIDs act via inhibition of the formation of prostanoids from arachidonic acid by COX. (5,6) Prostaglandins (and thromboxane, which is derived from PGH_2) are produced by all tissues as locally acting autacoids, and are important for many physiological functions in the GI tract, kidney, reproductive system and in platelets. (6) Prostaglandins are also key mediators of inflammation and pain, (6) and inhibition of their production by NSAIDs provides therapeutic benefit in many clinical conditions. However, NSAIDs pose a risk for GI, platelet and renal side effects because their mode of action results in unavoidable, mechanism-based adverse effects, (2-4) due to the concomitant reduction of inflammatory PGs and PGs important for normal physiological function. Recently, two distinct isoforms of COX were identified and designated COX-1 and COX-2. (6-9) These two isoforms are closely related and perform identical catalytic reactions with arachidonic acid, but the tissue distribution and regulation of expression of each are widely divergent.

Currently available NSAIDs inhibit both COX isoforms with negligible specificity in vitro (<10 fold). (1) COX-1 is constitutively expressed in most tissues throughout the body, including the GI tract, kidney, and platelets. (6,7) In contrast, COX-2 is normally expressed in very low amounts in healthy tissue, but is induced to high expression by inflammatory mediators (Figure 2). (8,9) Notably, the induced expression of COX-2 can be prevented by anti-inflammatory glucocorticoids. (11) The expression of COX-2 in association with inflammation, as well as pharmacological studies in animals, suggest that the therapeutic benefits of NSAIDs are largely due to the inhibition of COX-2. In contrast, the GI and platelet toxicity caused by NSAIDs is due to inhibition of COX-1, which is predominantly expressed in these tissues. Because COX-2 is constitutively expressed in the kidney, (12) the degree to which the renal effects of NSAIDs can be ascribed to COX-1 is uncertain, and studies in animals have not provided definitive information.

Figure 2. COX Isoforms



2.2.2 Beneficial Mechanism of Selective COX-2 Inhibition

The hypothesis presented in Figure 2 suggests that an agent which specifically inhibits COX-2, while sparing COX-1 activity, would provide the anti-inflammatory and analgesic activity of NSAIDs without their mechanism-based side effects. A number of studies in animal models with agents demonstrated to selectively inhibit COX-2 have supported this hypothesis. (10,13)

These observations led to the development of celecoxib, a potent and specific COX-2 inhibitor. Under a wide variety of in vitro conditions celecoxib demonstrates high selectivity for COX-2 (300 to over 2000 fold separation in inhibition curves vs. COX-1). The COX-2 specificity of celecoxib is due to an ability to occupy space within the active site of this isoform that is not present in COX-1. This unique binding to the active site results in the formation of a tight enzyme-inhibitor complex that is only slowly dissociable and non-competitive with substrate. In contrast, inhibition of COX-1 observed with high concentrations of celecoxib displays conventional competitive kinetics. The novel kinetic behavior of celecoxib noted in vitro translates to specific inhibition in vivo, i.e. in animals, concentrations/doses of celecoxib that maximally inhibit COX-2 derived PG formation have little or no effect on PG formation by COX-1 in platelets, kidney or the GI mucosa.

2.3 Intended Use

Celecoxib is intended for use in the treatment of the signs and symptoms of OA and RA and for the management of pain. The potential clinical benefits include antiarthritic and analgesic efficacy without UGI ulceration, ulcer complications or platelet dysfunction.

3.0 NONCLINICAL PHARMACOLOGY, TOXICOLOGY AND PHARMACOKINETICS

3.1 Nonclinical Pharmacology

Celecoxib was evaluated in a series of nonclinical pharmacology studies to: 1) examine its inhibitory kinetics and mechanism of action; 2) determine its anti-inflammatory and analgesic actions in animal models in vivo; and 3) specifically evaluate its propensity to cause GI tract injury and to explore its potential for action on a variety of physiological systems that are targets of NSAIDs. A major goal of these studies was to understand the pharmacological action of celecoxib in relation to its ability to produce differential inhibition of COX isoforms, in vitro and in vivo.

Celecoxib selectively inhibited COX-2 activity when tested in vitro on human recombinant COX-1 and COX-2. The two major metabolites of celecoxib did not inhibit either COX-1 or COX-2 in vitro, indicating that levels of celecoxib achieved in vivo likely determine the extent of COX-2 inhibition.

In other in vitro studies with whole blood, celecoxib inhibited lipopolysaccharide (LPS)-stimulated PGE_2 synthesis by monocytes (COX-2 mediated) at concentrations considerably lower than those needed to inhibit ionophore-stimulated synthesis of TxB_2 (COX-1 mediated). Celecoxib showed little ability to inhibit 5-lipoxygenase, the rate limiting enzyme for leukotriene synthesis in the other arm of the arachidonic acid metabolic pathway.

Celecoxib was evaluated in animal models known to be sensitive to NSAIDs, and which have been shown to be predictive of activity in humans. In an acute inflammation model, celecoxib caused dose dependent inhibition of swelling and hyperalgesia (pain) caused by an irritant, with maximal efficacy similar to that achieved with NSAIDs. Hyperalgesia was also rapidly reversed in this model by celecoxib, with a concomitant reduction in local inflammatory PG levels, as well as PG levels in cerebrospinal fluid. In a model of arthritis, celecoxib dose dependently reversed inflammation, local PG production and PG formation in cerebrospinal fluid. These data suggest that inhibition of COX-2 derived PG production by celecoxib is sufficient to achieve all of the anti-inflammatory and analgesic activity of mixed COX-1/COX-2 inhibitors (NSAIDs), and are consistent with the hypothesis that the therapeutic activity of the latter agents results

from inhibition of COX-2. Celecoxib also showed analgesic and anti-pyretic activity in other standard animal models.

In other studies in rodents, celecoxib was shown to have minimal effect on gastric PG production and did not cause GI lesions at doses >10 fold in excess of the maximal dose needed for anti-arthritic activity, and did not alter renal PG production as assessed in the urine.

3.2 Toxicology

A comprehensive non-clinical safety program designed to support clinical testing with celecoxib in chronic indications in adults has been completed. This program included toxicology studies for durations of up to six months in rodents and up to one year in dogs, and carcinogenicity studies conducted in rodents. Other studies were conducted to evaluate the acute lethal potential of celecoxib and adverse effects on physiological systems resulting from the pharmacological action of the compound. Potential reproductive toxicity was evaluated in studies that collectively addressed male and female reproductive function beginning with mating and early pregnancy through multiple generation assessments of reproductive performance. Mutagenic potential was evaluated in vitro using both mammalian and non-mammalian test systems; clastogenic potential was evaluated in vitro and in vivo. Other studies were conducted to characterize the irritation and antigenic potential of the compound.

In both rodents and dogs, the dose limiting toxicity observed in safety studies with celecoxib was related to the GI tract. At high doses and exposures of celecoxib, GI injury similar to that observed with NSAIDs was observed. The plasma concentrations/ exposures of celecoxib at which such injury was observed were similar in rats and dogs and were at least 4-to 9-fold higher than are needed to achieve maximal anti-arthritic activity in humans. This is consistent with the COX selectivity of celecoxib, i.e., at greater than therapeutic concentrations of celecoxib, COX-1 is inhibited and GI lesions ensue. This contrasts with NSAIDs, where therapeutic doses are lethal in rats and dogs. (14) Celecoxib did not cause renal papillary necrosis, dystocia, or affect hemostasis, all typical effects of NSAIDs. Celecoxib was not mutagenic and was not carcinogenic in rodents.

No evidence of toxicity or adverse pharmacological effects was produced by celecoxib in rats or dogs at the expected exposures and maximal plasma concentrations of the clinical doses (200 and 400 mg/day).

Based on the toxicity profile of celecoxib in animals, celecoxib is clearly differentiated from NSAIDs and is considered safe for use in humans.

3.2.1 Carcinogenicity

The carcinogenicity evaluation of celecoxib in mice was made at average exposures that were approximately 1- to 2.5-fold greater in males and 1- to 2-fold greater in females than the exposures at the clinical dose range. The carcinogenicity assessment of celecoxib in rats was made at average exposures throughout the study were as high as 4-9-fold greater in males and 5-10-fold greater in females than the exposures produced by the range of clinical doses.

Carcinogenicity evaluations in rats and mice revealed no evidence of carcinogenicity or increases in the incidence of background tumors after 104 weeks of dosing.

3.2.2 Reproductive Toxicity

Celecoxib does not produce any effect on fertility or male reproductive function in rats. Assessments of reproductive function and early embryonic development show that decreased embryonic viability reflected as pre- and post-implantation loss is produced by the compound at dosages greater than 50 mg/kg/day, which produced exposures greater than therapeutic exposures (5-11-fold the area under the plasma concentration-time curve from 0-24 hours at the range of clinical doses). The same effects are seen with NSAIDs. This is the likely consequence of disruption of prostaglandin-dependent processes involved in early reproductive function and the establishment of pregnancy. No evidence of an effect on ovulation was observed, but the finding of dose-dependent decreases in numbers of implantation sites and increases in resorptions suggest that, in the rat, implantation and maintenance of pregnancy may be affected by celecoxib. The effects are expected given the pharmacological action of the compound (i.e., PG inhibition) and are not due to permanent alteration of female reproductive function.

Teratology evaluations conducted in rabbits did not reveal evidence of teratogenicity for celecoxib at dosages up to 150 mg/kg/day. A higher dosage (300 mg/kg/day) produced post-implantation loss.

Studies in rats confirmed that celecoxib crosses the placenta and is available to the fetus. Diaphragmatic hernia was observed in one of two teratology studies conducted in rats at exposures that were at least 7-fold greater than the exposure associated with the maximum clinical dose, 400 mg/day. This malformation is not the same as the more severe presentation involving lung malformations typically seen congenitally in humans; this effect is not regarded as a teratogenic mechanism, but rather as an exacerbation of the background incidence of this malformation in the rat.

The dosages used in the perinatal evaluation produced evidence of maternal toxicity in the F_0 females as mortality related to GI lesions and/or peritonitis and decreased feed consumption in the higher dose groups. The length of gestation was slightly but significantly increased for all celecoxib-treated groups but not in a dose-dependent manner and all gestation periods were within historical control data ranges. There was no evidence of dystocia or increased parturition time. There was no evidence of an effect of celecoxib on the physical appearance of the pups with the exception of diaphragmatic hernias discussed previously but at a lower incidence than in the teratology study. There was no evidence of significant effects on the physical development, survival, behavior and reproductive performance of the F_1 generation or on the development and survival of the F_2 generation pups resulting from treatment of the F_0 females with celecoxib.

3.2.3 Mutagenicity

Celecoxib produced no evidence of mutagenicity in vitro in bacteria (Ames assay) or mammalian cells. Both assays evaluated concentrations of celecoxib that were delimited by cytotoxicity or signs that the solubility limits of the compound had been exceeded. No evidence of mutagenic potential, clastogenicity, or potential for disruption of the mitotic apparatus was detected in vivo; and no direct signs of clastogenicity were observed in vitro. The positive and negative controls for all assays yielded the expected results, thus validating the integrity of the test systems and establishing that celecoxib is not genotoxic. This conclusion is consistent with the absence of carcinogenicity in the cancer bioassays.

3.3 Nonclinical Pharmacokinetics

Nonclinical assessment of the PK of celecoxib was conducted in five species. Celecoxib is well absorbed following oral administration to animals with an absolute bioavailability of 60-90%. The apparent volume of distribution of celecoxib was approximately 2 to 3 L/kg and was consistent across the species examined. This volume is greater than total water volume and suggests the drug is readily available to tissues. Celecoxib was eliminated rapidly from the plasma of guinea pig, cynomolgus monkey and rhesus monkey with half-lives of 1-2 hours. Celecoxib crosses the placenta and is available to the fetus. Celecoxib is excreted in rat milk at concentrations similar to those in serum.

THIS PAGE INTENTIONALLY LEFT BLANK

4.0 HUMAN PHARMACOKINETICS

Pharmacokinetic data were obtained from over 1500 subjects/patients who received single or multiple oral doses of celecoxib in 32 clinical studies (Table 1).

Table 1. Summary of Celecoxib Pharmacokinetic Studies

Type of Data	Study	Basic PK Profile	No. of Subjects
Basic PK Profile	001	Single-dose Safety/Tol/PK	52
	400	Single-dose Safety/Tol/PK (Japan)	30
	003	Multiple-dose Safety/Tol/PK	24
	004	Multiple-dose Safety/Tol/PK	24
	401	Multiple-dose Safety/Tol/PK (Japan)	6
	006	[^{14}C]-Celecoxib ADME	8
	019	Food and Antacid Effects	24
	026	Platelet Effect/PK 400 mg BID	6
	032	Total vs. Unbound Conc.	8
	037	Capsule vs. Suspension Bioavail.	36
	043	BID vs. QD Dosing	24
	065	Platelet Function/PK 600 mg BID	12
	069	AM vs. PM QD Dosing	24
	088	Fed/Fasting 50 mg vs. Fed/Fasting 100 mg	24
Special Populations	010	PK/Renal Effect in Elderly	24
	015	Elderly vs. Young PK	48
	016	PK in Hepatic Impairment	46
	036	PK in Chronic Renal Failure	22
	012	PK in RA	181
	013	PK in OA	170
	824	Population PK Phase III (studies 020 and 023)	110
	826	Dental Pain PK/PD (studies 005, 025, 027, 070)	427
Drug-Drug Interactions	017	Methotrexate Interaction	14
	038	Lithium Interaction	24
	072	Fluconazole/Ketoconazole Interaction	35
	040	Warfarin Interaction	12
	050	Phenytoin Interaction	16
	051	Tolbutamide Interaction	16
	039	Glyburide Interaction	24
Bioquivalency of Clinical Trial and Commercial Formulations	018	Phase II vs. Phase III 200 mg	24
	044	Phase III vs. Commercial 200 mg	24
	084	2*100 mg Phase III vs. 2*100 mg Commercial vs. 1*200 mg Commercial	47

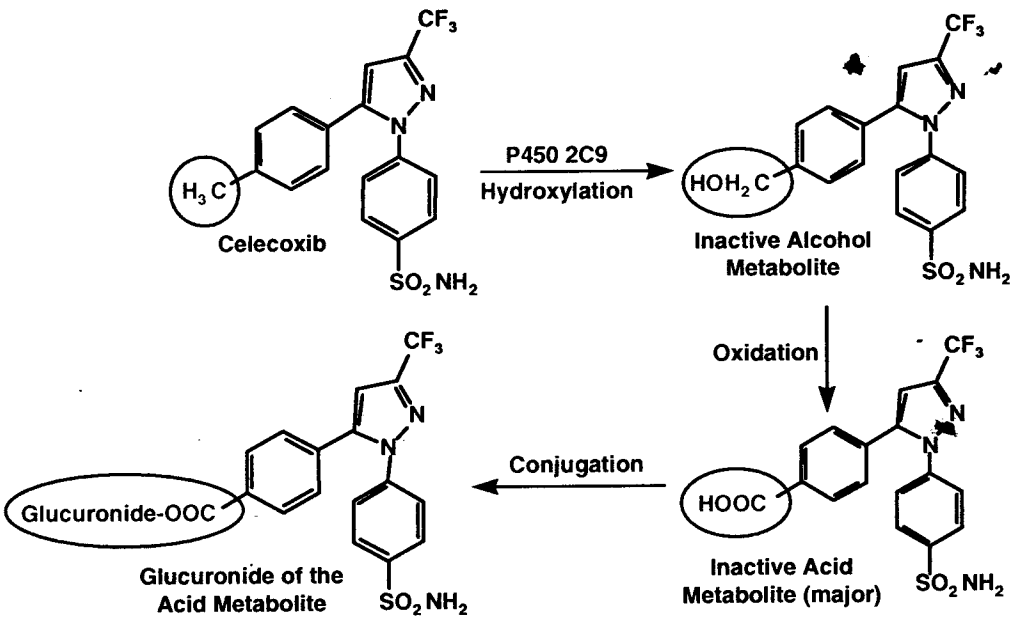
4.1 Pharmacokinetic Profile

Celecoxib has an apparent plasma clearance of ~500 ml/min (30 L/hr) adjusted for 70 kg body weight in young healthy adults following single dose administration. It has a protein binding in vivo of about 97% and this binding remains constant within the wide therapeutic concentration range of the total drug. It is equally distributed between plasma and erythrocyes. The apparent volume of distribution of celecoxib was ~500 L/70 kg after a single 200 mg dose in young healthy adults, suggesting extensive tissue uptake. The plasma elimination half life of celecoxib is ~10-12 hr. The absorption of celecoxib is slightly increased when taken with food and slightly decreased in the presence of antacids. These effects, however, are not considered clinically important and do not require dose adjustment. There is also circadian variation in the absorption of celecoxib resulting in slower absorption of the drug after evening dosing compared to morning dosing. Time of once-daily celecoxib administration (morning vs. evening) did not affect total drug exposure over 24 hours. However, once-daily dosing in the evening resulted in a slower rate of absorption and would be expected to provide higher drug concentrations in the morning.

4.2 Metabolism

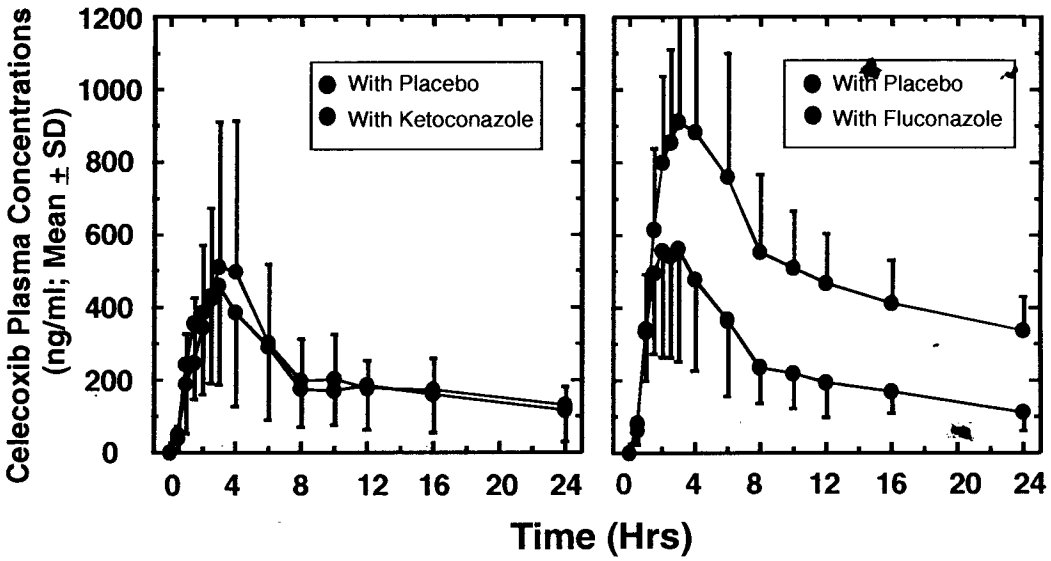
Celecoxib is extensively metabolized in man and none of the metabolites is pharmacologically active (Figure 3). The percentage of dose excreted in feces as unchanged drug is only 2.6% and no unchanged drug was detected in urine.

Figure 3. Metabolic Profile of Celecoxib



The major excreted material is the inactive acid metabolite which constitutes ~19% of the dose in the urine and ~54% in the feces. This acid metabolite is formed from the initial and the rate determining hydroxylated metabolite. Both in vitro and in vivo studies indicate that this hydroxylation pathway is mediated predominantly via cytochrome P450 2C9. This was demonstrated clinically by assessing the metabolism of celecoxib in the presence of the cytochrome P450 3A4 inhibitor ketoconazole (200 mg QD for seven days) or the cytochrome P450 2C9 inhibitor fluconazole (200 mg QD for seven days) (Figure 4). Ketoconazole treatment did not markedly increase plasma concentrations of celecoxib whereas fluconazole produced nearly a two-fold increase in the area under the curve of celecoxib.

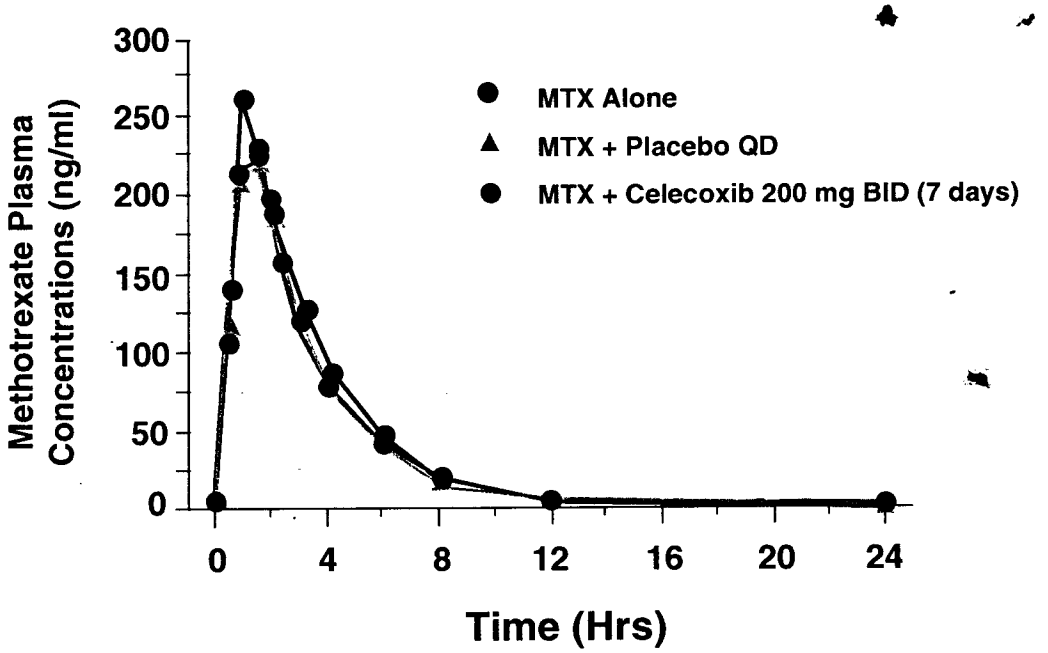
Figure 4. Effects of Multiple Oral Doses of Ketoconazole and Fluconazole on the Single-Dose PK of Celecoxib: Study 072



4.3 Drug-Drug Interactions

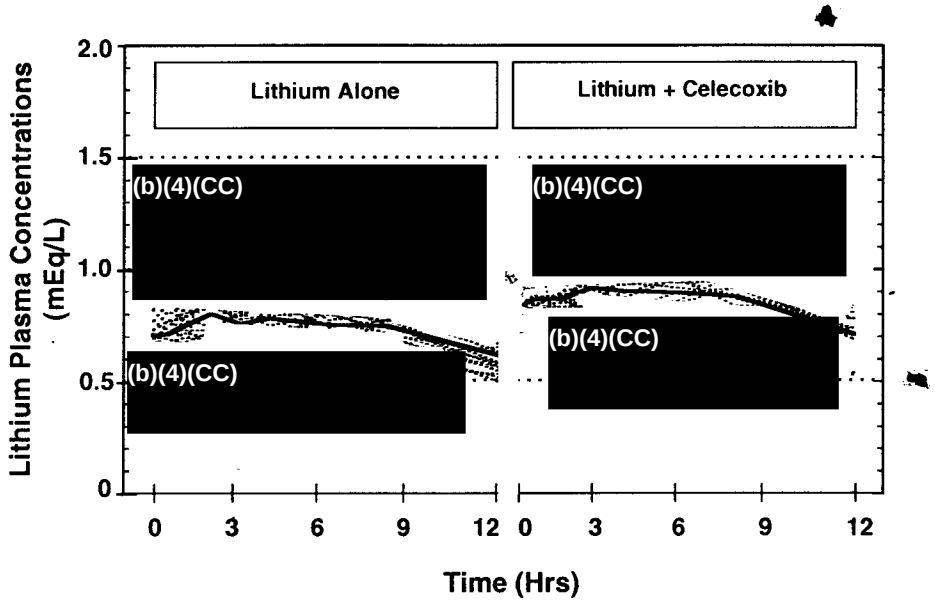
Drug-drug interaction studies were done to examine the effects of multiple doses of celecoxib on the PK of other known substrates of cytochrome P450 2C9 with narrow therapeutic windows. The cytochrome P450 2C9 substrates chosen were tolbutamide, phenytoin, glyburide and warfarin. It is noteworthy that all of these drugs have been reported to interact with some of the presently available NSAIDs. Because of their COX-1 mediated effect on the kidney, some of the NSAIDs have also been reported to decrease the renal clearance of those drugs that are predominantly eliminated via the kidney. (4) Effects of celecoxib on the renal clearance of methotrexate and lithium were therefore also examined. Celecoxib administered as 200 mg twice a day (BID) for seven days did not significantly affect the kinetics of methotrexate (Figure 5).

Figure 5. **Effect of Multiple Oral Doses of Celecoxib on Methotrexate PK in Rheumatoid Arthritis Patients Receiving Weekly Oral Doses of Methotrexate: Study 017**



Serum concentrations of lithium increased slightly (17%) when coadministered with celecoxib (200 mg BID for seven days) but this increase was not considered clinically important (Figure 6). In all subjects who received lithium and celecoxib, lithium plasma concentrations did not exceed the upper range of therapeutic lithium concentration (1.5 mEq/L).

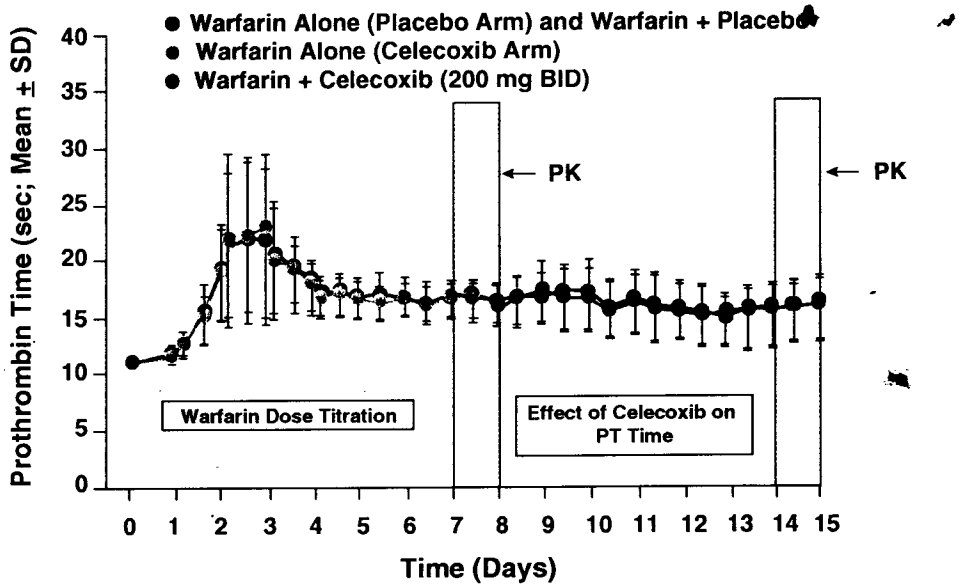
Figure 6. Effect of Multiple Oral Doses of Celecoxib on the Steady State PK of Lithium: Study 038



Ranges for normal limits are shown by dotted lines

Multiple doses of celecoxib also showed no clinically important interactions with other substrates of cytochrome P450 2C9, namely phenytoin, glyburide, tolbutamide and S-warfarin. Figure 7 shows no change in prothrombin time following multiple doses of warfarin administered with placebo compared to warfarin adminstered with celecoxib 200 mg BID for seven days.

Figure 7. **Prothrombin Time vs. Time Relationship Following Administration of Racemic Warfarin During Dose Titration Phase and During Placebo or Celecoxib Coadministration: Study 040**



4.4 Pharmacokinetics in Special Populations

The clearance of celecoxib is lower (higher drug exposure [area under the plasma concentration-time curve]) in elderly women and in patients with moderate hepatic impairment (Figures 8 and 9). The reduction in clearance seen in elderly females (>65 years) in the PK studies can be partly attributed to age and partly to their lower body weight. However, the decrease in clearance in healthy elderly Caucasians is <40% compared to healthy Caucasians <50 years. Population PK analysis of patients included in the pivotal arthritis efficacy trials indicated that body weight and race had important influences on the clearance in OA and RA patients. Celecoxib clearance is not markedly reduced in patients with stable chronic renal dysfunction (glomerular filtration rate [GFR] >34 ml/min/1.73 m^2) and in patients with Type II non-insulin dependent diabetes mellitus (NIDDM).

Figure 8. **Steady State Plasma Concentrations in Patients with Mild and Moderate Hepatic Impairment and Their Matching Controls: Study 016**

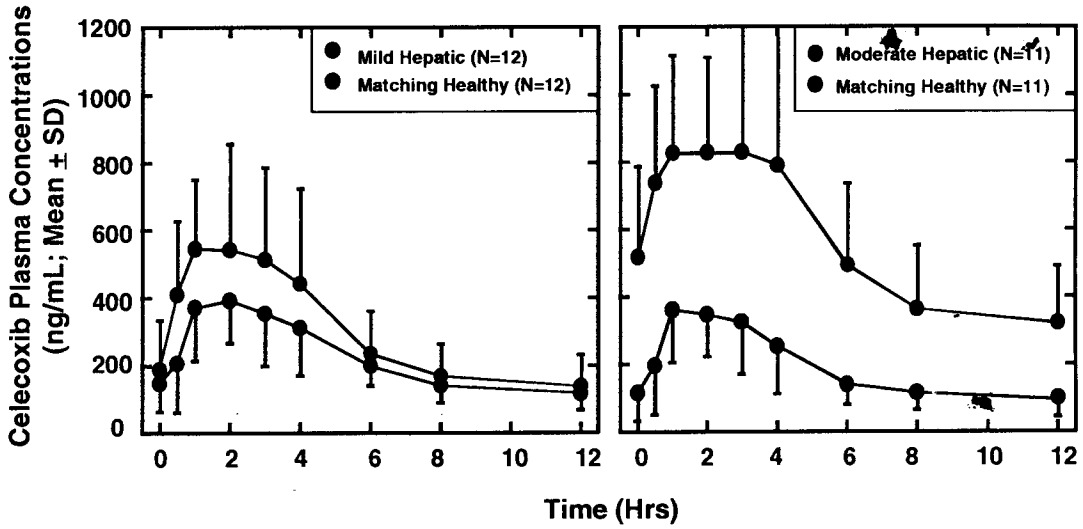
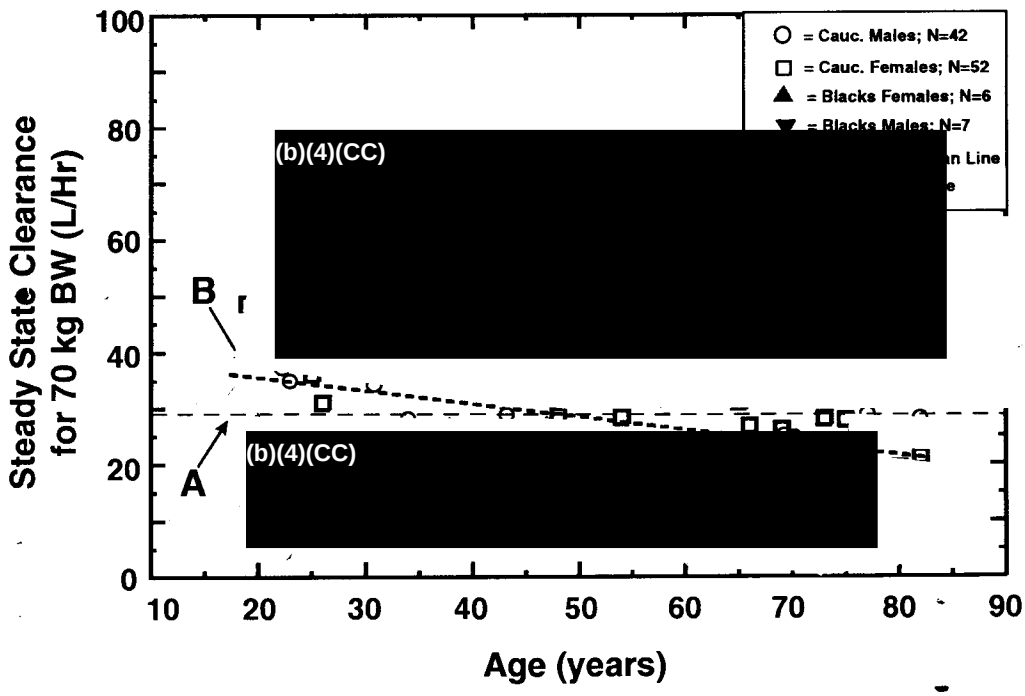


Figure 9. **Relationship Between Age and 70 kg Body Weight Adjusted Steady State Clearance Following 200 mg BID Administration of Celecoxib Given with Food: Studies 010, 015, 017, and 043**



5.0 CLINICAL EFFICACY

5.1 Efficacy in Osteoarthritis

Eleven studies, five pivotal, five supportive, and one open-label, long-term safety study were conducted in patients with OA to provide evidence of the efficacy of celecoxib for the treatment of the signs and symptoms of OA (Table 2). The data presented in this section are primarily from the pivotal OA efficacy trials (Studies 020, 021, 054, 060, and 087), which were all double-blind, placebo-controlled trials of 6 or 12 weeks duration, and enrolled 200 or more patients per treatment. The five supportive controlled trials (Studies 013, 047, 042, 062, and 071) are each summarized briefly.

Table 2. Summary of Celecoxib OA Studies

Study No. - Population	Duration	No. of Patients	Treatments
Pivotal Studies			
020 - Knee OA flare	12 weeks	1093	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
021 - Knee OA flare	12 weeks	1215	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
054 - Hip OA flare	12 weeks	1061	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
060 - Knee OA flare	6 weeks	686	Celecoxib 100 mg BID or 200 mg QD or placebo
087 - Knee OA flare	6 weeks	718	Celecoxib 100 mg BID or 200 mg QD or placebo
Supportive Controlled Studies			
013 - Knee OA flare	2 weeks	293	Celecoxib 40, 100, or 200 mg BID or placebo
047 - Knee OA flare	4 weeks	402	Celecoxib 25, 100, or 400 mg BID or placebo
042 - Hip or knee OA	6 weeks	688	Celecoxib 100 mg BID or diclofenac 50 mg BID
062 - OA or RA	12 weeks	537 (389 OA)	Celecoxib 200 mg BID or naproxen 500 mg BID
071 - OA or RA	12 weeks	1099 (812 OA)	Celecoxib 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID
Open-Label Study			
024 - OA or RA	1-2 years	4499 (2554 OA)	Celecoxib 100-200 mg BID for OA

5.1.1 Pivotal OA Efficacy Studies: Studies 020, 021, 054, 060 and 087

5.1.1.1 Population and Design

Each of the three 12-week pivotal studies (Studies 020, 021, and 054) was a randomized, multicenter, double-blind, active- and placebo-controlled comparison study of the efficacy and safety of celecoxib 50 mg BID, 100 mg BID, and 200 mg BID and naproxen 500 mg BID in patients with OA of the knee (Studies 020 and 021) or hip (Study 054).

The two 6-week pivotal studies (Studies 060 and 087) were conducted to assess whether a once-a-day dose regimen was appropriate and both were randomized, parallel group, multicenter, double-blind, placebo-controlled studies comparing the efficacy of celecoxib 200 mg QD to celecoxib 100 mg BID in patients with OA of the knee.

In all pivotal studies, patients were to be in an OA flare at the Baseline Visit. The criteria for demonstrating OA flare depended on whether the patient was in Category 1 (i.e., currently receiving NSAID or analgesic therapy for his/her OA) or Category 2 (i.e., not receiving NSAID or analgesic therapy and had uncontrolled OA).

For patients in Category 1, an OA flare was demonstrated if both the Baseline Patient's and the Physician's Global Assessment of Arthritic Condition were rated as "fair," "poor" or "very poor" and the Baseline arthritis assessments met at least three of the following four criteria:

1. Patient's Assessment of Arthritis Pain (Visual Analog Scale [VAS]) measurement of at least 40 mm (on a 100 mm scale);
2. An increase from the screening assessment of two or more points in the OA Severity Index (on a 24 point scale);
3. An increase from the screening visit of one or more grades in the Patient's Global Assessment of Arthritic Condition (on a 5 point scale);
4. An increase from the screening visit of one or more grades in the Physician's Global Assessment of Arthritic Condition (on a 5 point scale).

For patients in Category 2, an OA flare was demonstrated if they met at least three of the following four criteria during the Baseline arthritis assessments:

1. Patient's Assessment of Arthritis Pain (VAS) measurement of at least 40 mm;
2. The OA Severity Index was ≥7;
3. The Patient's Global Assessment of Arthritic Condition was "poor" or "very poor";
4. The Physician's Global Assessment of Arthritic Condition was "poor" or "very poor."

5.1.1.2 Scales Used for Measurement of OA Efficacy

The analysis of celecoxib's efficacy in the treatment of the signs and symptoms of OA incorporated data from a large number of primary and secondary endpoints.

The primary OA efficacy endpoints included the following:

- Patient's Assessment of Arthritis Pain - VAS (15)
- Patient's Global Assessment of Arthritic Condition (16)
- Physician's Global Assessment of Arthritic Condition (16)
- WOMAC (Western Ontario and McMaster Universities) OA Index (Composite score and subscores for pain, joint stiffness, and physical function) (17)

The final list of secondary OA efficacy endpoints included the following:

- Functional Capacity Classification (18)
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- OA Severity Index (OASI) (19)
- APS (American Pain Society) Pain Measure (in 12-week pivotal OA studies only) (20)
- Patient Assessment of Function

In addition, the SF-36 Health Survey was used to obtain quality-of-life information. (21)

Primary efficacy evaluations were measured at Baseline, Weeks 2, 6, and 12 (or Early Termination) in each of the 12-week pivotal studies and at Baseline and Weeks 2 and 6 (or Early Termination) in each of the 6-week pivotal studies. The WOMAC OA Index was measured at Baseline, and Weeks 2 and 12 in each of the 12-Week pivotal studies and Baseline and Week 6 in each of the 6-week pivotal studies.

The primary population for analysis was the Intent-to-Treat (ITT) cohort which was defined as all randomized patients who took at least one dose of the study drug. The last observation carried forward (LOCF) method was used for imputing missing values.

The Patient's and Physician's Global Assessments of Arthritic Condition were made independently and were graded on a 5 point scale (5-very poor, 4-poor, 3-fair, 2-good, or

1-very good). The Patient's Assessment of Arthritis Pain - VAS was assessed for patient-identified "Index Joint" (i.e., the hip or knee with the most symptoms of OA). Patients assessed the amount of arthritis pain in the "Index Joint" on a 100 mm line VAS with the 0 mm point indicating no pain and 100 mm point indicating the most severe pain. The WOMAC OA Index is a tri-dimensional, self-administered questionnaire. The patient responded to 24 component items: 5 regarding pain, 2 regarding stiffness, and 17 regarding physical function.

Mean change from baseline analyses using analysis of covariance models were performed for Patient's Assessment of Arthritis Pain and the WOMAC OA Index. For Patient's and Physician's Global Assessments, patients were classified into 'Improved,' 'No Change', and 'Worsened' categories based on a two grade change criterion. Improvement was defined as reduction of at least two grades from Baseline for grades 3-5 or a change in grade from 2 to 1. A categorical analysis based on the Cochran-Mantel-Haenszel test was performed for treatment comparisons.

5.1.1.3 Patient Disposition

A total of 3255 patients with OA of either the hip or knee were entered into one of the three 12-week pivotal studies (020, 021, and 054), were randomized to receive one of five treatments: celecoxib 50 mg BID, celecoxib 100 mg BID, celecoxib 200 mg BID, naproxen 500 mg BID, or placebo, and were included in the ITT cohorts. Table 3 presents a summary of all patients, by treatment group, who completed one of the three 12-week pivotal studies. The reasons for study termination are also summarized in this table.

Table 3. Reasons for Study Termination: 12-Week Pivotal OA Studies 020, 021, and 054

	Number of OA Patients by Treatment Group				
		Celecoxib			Naproxen
Study	Placebo	50 mg BID	100 mg BID	200 mg BID	500 mg BID
Study 020 (a)	**(N=204)(b)**	**(N=203)**	**(N=197)**	**(N=202)**	**(N=198)**
Total Completed	**91 (45%)**	**118 (58%)**	**116 (59%)**	**129 (64%)**	**116 (59%)**
Total Withdrawn	**113 (55%)**	**85 (42%)**	**81 (41%)**	**73 (36%)**	**82 (41%)**
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)
Adverse Event	16 (8%)	18 (9%)	31 (16%)	21 (10%)	18 (9%)
Other	18 (9%)	6 (3%)	10 (5%)	3 (1%)	12 (6%)
Study 021 (a)	**(N=242)**	**(N=252)**	**(N=240)(b)**	**(N=233)**	**(N=226)**
Total Completed	**119 (49%)**	**168 (67%)**	**165 (69%)**	**154 (66%)**	**147 (65%)**
Total Withdrawn	**123 (51%)**	**84 (33%)**	**75 (31%)**	**79 (34%)**	**79 (35%)**
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)
Adverse Event	14 (6%)	16 (6%)	16 (7%)	23 (10%)	30 (13%)
Other	20 (8%)	12 (5%)	8 (4%)	7 (3%)	9 (4%)
Study 054	**(N=218)(b)**	**(N=216)**	**(N=207)**	**(N=213)**	**(N=207)**
Total Completed	**79 (36%)**	**111 (51%)**	**111 (54%)**	**119 (56%)**	**118 (57%)**
Total Withdrawn	**139 (64%)**	**105 (49%)**	**96 (46%)**	**94 (44%)**	**89 (43%)**
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)
Adverse Event	16 (7%)	7 (8%)	27 (13%)	25 (12%)	29 (14%)
Other	10 (5%)	12 (6%)	8 (4%)	14 (7%)	9 (4.3%)

a) Includes only patients with OA of the knee. Eighty-nine patients with OA of the hip were enrolled in Study 020; 22 patients with OA of the hip were enrolled in Study 021.

b) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]), who were randomized into a study but did not receive study medication and are not included in the ITT cohort.

A total of 1399 patients with OA of the knee were entered into one of the two 6-week pivotal studies, were randomized to receive one of three treatments (celecoxib 100 mg BID, celecoxib 200 mg QD, or placebo), and were included in the ITT cohort. Table 4 presents a summary of all patients, by treatment group, who completed one of the 6-week pivotal studies. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.